IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

CENTOCOR, ET AL	*	Civil Docket No.
	*	2:07-CV-139
VS.	*	Marshall, Texas
	*	
	*	June 22, 2009
ABBOTT LABORATORIES	*	1:35 P.M.

TRANSCRIPT OF TRIAL PROCEEDINGS
BEFORE THE HONORABLE JUDGE T. JOHN WARD
UNITED STATES DISTRICT JUDGE
AND A JURY

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P R O C E E D I N G S

COURT SECURITY OFFICER: All rise.

THE COURT: Please be seated.

Let's continue, Counsel.

MS. ELDERKIN: Thank you, Your Honor.

JOHN GHRAYEB, PLAINTIFFS' WITNESS, SWORN

DIRECT EXAMINATION (CONTINUED)

BY MS. ELDERKIN:

Q. Dr. Ghrayeb, before the lunch break, we were talking about your patent, which is in the jury notebook. It's a rather lengthy document.

I wonder if you could just generally go through the patent and tell the jury what the different parts of a patent are in there.

A. As you go through the patent, it starts by putting name of the inventors and history of the patent. Then it starts publications that may be relevant.

Then what you see are these figures here which represent all the actual data that was generated by the scientists in the lab. And throughout the patent, they will refer to these -- these figures.

Then when you get past that, you get to the background of the invention. And I'm not sure I can do it as well as His Honor did, but the summary of the invention, which tells you in general how -- what we're claiming what this patent is about.

Then it goes through a -- you see starting in the Columns 7 and 8, descriptions of those figures. And then after that, they start talking about a detailed description of the invention. And this goes into great detail on how we performed the work to create the invention, and also, you know, gives information to anybody who has skills in this field that work in labs to be able to follow these instructions and be able to reproduce exactly what we did.

And then you start on -- later on about giving

examples, detailed examples of what we did. And then it also later on talks about -- you know, includes what other methods you can use to, you know, make the same type of antibody. Talks about how the product worked in the clinic. It gives a description of that.

So all these examples are meant to describe, in great detail, what this invention is, what it's capable of doing so that anybody who can read this, it's almost like to be able to, you know, follow this and, you know, be able to reproduce it.

Q. Dr. Ghrayeb, let's look at some of the parts of the patent in a little bit more detail now.

Can I refer you to Column 5; that's the column that has a 5 at the top, under the heading, Summary of the Invention, from about Lines 45 to 59.

MS. ELDERKIN: Yeah, if you could blow up 49 to 59, Mr. Ficocello, and then particularly the third paragraph there.

Q. (By Ms. Elderkin) Can you tell the jury what that third paragraph says? Paraphrase it; obviously not to read it. Just tell them what that says.

A. Sure.

What it says is that these anti-TNF antibodies, the antibodies to TNF, includes many monoclonal antibody that could be part rodent, part

human. It can be fully rodent, like in a mouse; could be human antibodies or any pieces of that antibody. The key thing is it has at least one part of it that binds, which is the variable region, which binds to TNF.

Q. So is this part of your summary of the invention saying that the antibodies could include chimeric antibodies, rodent antibodies, and human antibodies?

A. That's correct.

Q. And do you know when the reference here to human antibodies was added to your applications in that series of applications we talked about before lunch?

A. I believe that was in -- sometime in '93, this was included.

Q. Let's look at -- if we could, look at the first page of your patent.

A. Yes.

Q. Again, where it says the references or the related family.

A. Yes.

Q. And you can see that there are --

MS. ELDERKIN: If you could page down, Mr. Ficocello, and highlight the related U.S. applications.

Q. (By Ms. Elderkin) You see, there was an

application filed in February of 1993, and then there's also one filed in February of 1994?

A. Right.

Q. And do you remember when the reference to rodent -- to human antibodies was added?

A. I believe it's in 1993.

Q. Would you look at your patent -- is there a chance that it could be February of 1994, Dr. Ghrayeb?

A. You know, there's so many patents that -- you know, if I had that recollection, it could be, yes.

Q. Okay.

MS. ELDERKIN: I'll ask for somebody to get the 1994 application out so we can show Dr. Ghrayeb, please.

Q. (By Ms. Elderkin) While we're doing that, would you look at Figures 16A and 16B, please.

What do all those letters mean in that figure, 16A and 16B?

A. These are the -- a sequence of the building blocks for the light chain variable region and the heavy chain variable region, which I showed you on the figure earlier.

Q. Okay. And what does that mean?

A. What -- what it means is we've identified in great detail what the building blocks, the sequence of

the A2 -- cA2 antibody that is responsible for binding to TNF.

Q. And why is this of use to anybody?

A. I think this is -- this is the ultimate way you can -- if you wanted to replicate, you know, the invention, you can see how close you can get to the -- you know, the actual invention.

It's really important for people, you know, trying to replicate it to know exactly what the sequence is.

Q. Okay. And was the sequence for the variable region of cA2, how did that compare to the sequence for the variable region of A2, the mouse antibody?

A. It's identical.

Q. Okay. If we could look further on in your patent to Column 16, the column that has the No. 16 on top. And going back a third of the way down Column 16 there's a heading, Recombinant Expression of Anti-TNF Antibodies.

Can you explain for the jury, please, what's described in this section under that heading starting at Column 16?

A. This describes how the -- you could produce an express in the lab, an antibody, to -- that would bind to TNF-alpha. So -- I mean, it goes through, you know,

a lot of details about how you would obtain the DNA.

I mentioned earlier that you went into the cell, how you obtain the DNA, what you do to characterize it, and then, you know, how would -- you would link it, then, with a human constant region to make a full antibody.

And it talks about, you know, different methods that you could use for that purpose.

Q. So is it fair to characterize the discussion starting at Column 16 in this section as disclosing different ways of making antibodies according to the invention?

A. That's correct.

Q. Okay. Let's look at Column 18, please. And we're going to look at the paragraph that starts at Line 29 and goes to the bottom of that page.

What is disclosed in this paragraph, Dr. Ghrayeb?

A. This talks about an alternate way to do the cloning. In other words, through the recombinant DNA to find the antibody variable regions. It talks about getting the genes from the cells, making libraries, screening libraries, different ways to do that.

Q. And in simpler terms, is it fair to characterize this as disclosing how to get the DNA

instruction booklet for the variable region of the antibody?

A. That's right.

Q. Okay.

MS. ELDERKIN: If we could blow up the section that's at Column 19 -- at Column 18, Lines 48 to 53, please.

Q. (By Ms. Elderkin) And what did you disclose here?

A. Here, we disclose yet another method that people could use to achieve what we achieved, and that is using what's known as phage display. It's another method that you can use to take the genes out of the cells and then use that technique to then try to identify which one of these is responsible, can be identified as binding to a target like TNF.

Q. Okay. Now, one of the articles that's cited here at Lines 52 to 53 is an article, Marks et al, and it says October 1993.

Does that date refresh your recollection as to when this was added to your patent application? Was it February '93 or February '94?

A. Yes. This was in February of 1994.

Q. Okay. Now, do you remember the Marks article that you've cited here that we just highlighted?

A. Yes. I was following the field, you know, the entire field, so I remember that paper.

Q. Okay. Could you please look at Defendants' Exhibit 381?

Is this the Marks 1993 article that you cite in your patent?

A. Yes.

Q. Okay. What did this Marks 1993 article disclose?

A. What this paper describes is making -- using phage library to make -- to identify antibodies that bind to red blood cells.

So a library is made from DNA from human source, and then this library is screened to look for antibodies that are bound to, you know, those particular cells. And then the antibodies were characterized in the paper.

Q. A little bit more generally, what, if anything, does this article disclose about whether or not phage display technology could be used to create human antibodies?

A. Right. In the introduction of the paper, Dr. Marks and the others disclose that antibodies to -- human antibodies to self and non-self antigens have been obtained, you know, in the past.

Now, what that means is that you can use these libraries to look for antibodies that self means that the -- your body normally thinks as one of their own, not just foreign proteins. So something like human TNF would be considered as one of those targets where you can find antibodies using this technique.

Q. Now, the human variable region that is talked here in the Marks article, that's not the whole antibody, right?

A. No, it's not.

Q. So how does this relate, then, to making human antibodies, full antibodies?

A. This phage display cannot be used to make -- you know, find -- make full human antibodies. You would have to take that variable regions that you find in that library and use the techniques that we did to then cut and paste it to a human constant region to make, then, an antibody that's complete, that will have a human variable region and then a human constant region.

Q. Now, in the -- on the first page of the article, the first sentence of the second paragraph, there's a sentence we're going to highlight. It says: Phage display has been used to produce human antibody fragments against self and non-self antigens without deliberate immunization.

Do you know what a reference to self and non-self antigens means here?

A. Yes. A self-antigen -- and this is talking about a particular species. Let's take human.

So a self-antigen would be a protein that you make yourself in your body. And then when we give it to you, you recognize it as self, and, therefore, don't consider it to be foreign.

Non-self would mean if I gave you a -- injected you with a mouse antibody, that would be, you know, a foreign protein.

So that's the self and non-self.

Q. Okay. How at all does that relate to TNF antibodies?

A. Well, what -- what that means is that using this technique, you can make antibodies to proteins that your body considers your own, self-proteins. Like tumor necrosis factor is a protein that you make normally. So this technique has been shown to produce antibodies against those proteins, even though, you know, they are considered to be, you know, human proteins that you normally wouldn't consider as foreign.

Q. Let's go back to Column 18 of your patent, please.

MS. ELDERKIN: And if we can highlight

Line 60, 6-0, and a few sentences around it.

Q. (By Ms. Elderkin) At Line 60, there's a reference to a human anti-TNF variable region.

Do you know when that language was added to your patent application?

A. I believe it's '94.

Q. Okay. And what does that reference mean, referring to human anti-TNF variable region there?

A. As I explained earlier, the business end of the antibody is the variable region that's responsible for the binding, and that is really the important part. So this can be obtained from a human source, from human DNA. It can be obtained from a mouse DNA. And it would do the same -- the same final thing that an antibody would do is bind to TNF. So it doesn't matter where it came from, whether it's from human source.

If it has the right specificity, has the right sequence, it will bind to the human TNF.

Q. Okay. Let's look at Columns 33 and 34 of your patent, please, under the heading, Structural Analogs of Anti-TNF Antibodies and Anti-TNF Peptides.

A. Yes.

Q. So what's described in this section of your patent?

A. This describes a technique that you could use

to improve upon an antibody that you might have isolated from some source, and you wanted to make it, you know, bind to your target TNF, for example, much more tightly. So you can use techniques to -- actually, it's almost like having a microscope and being able to look at the structure in three dimensions, and be able to look at those building blocks where they are in the protein, where they are in the target, and then what you can see is how they're binding, how the antibody is binding to the target.

Then using the computer modeling, you can then change some of these building blocks to allow the antibodies to bind even more strongly to the TNF or any of the protein that you're interested in.

Q. So if I were to get a human variable region using the technology we just discussed that you cited in Column 18, how would this disclosure at Columns 33 and 34 be relevant, if at all, to improving that -- the binding of that variable region?

A. Yeah. That's -- I mean, the technique here is used to accomplish what's known as affinity maturation, which is, you know, to take an antibody and improve its affinity, meaning its ability to bind. So this is one -- one technique described on how you could do that.

Q. And does that have to do anything with the

amino acid building blocks in the variable region?

A. Yes.

Q. What does it have to do with that?

A. What you are doing then is changing those building blocks, the ones that, you know, naturally occur in the DNA, and you actually can, you know, change them, put amino acids that you think, or the computer model helps you think would be better than the ones that you had there originally.

Q. Okay.

MS. ELDERKIN: Could we look, please, at Column 34, Lines 26 to 33?

Q. (By Ms. Elderkin) What does this say about affecting or not affecting the binding affinity, the ability of the antibody to bind?

A. Yeah. So what this section is saying is using the information that you obtain, you can then make different what's known as analogs, or different versions of your variable region, to substitute the building blocks with different ones so that the -- the -- you then increase the affinity or the ability of the antibody to bind to TNF in this case.

So that's -- the whole point of this is to change the way that the antibody interacts with TNF, change those building blocks. And the new ones you put

in allow the antibody to bind more tightly to TNF.

Q. And --

A. And that's the desirable thing.

Q. And those techniques could be used with a variable region, a human variable region, that you got using phage display?

A. There is no difference.

Q. This section that we've been talking about in Columns 33 to 34, when was that added to your patent application?

A. That was added in February '94.

Q. Okay. Let's move on to Column 36 of your patent, please, Lines 3 through 12.

And what are you disclosing here in your patent?

A. What we're talking about is how, you know, we actually can administer those -- those antibodies. So it talks about taking the antibodies and then injecting them into a patient. And then you can do it in different ways.

I mean, you can give it -- I can't give it to you as a pill, because, you know, your stomach would destroy protein. That's what it's supposed to do. But what you can do is give it by intravenous injection, which is -- you know, most of you know what intravenous

is.

You can also give it by subcutaneous, which means, you know, under the skin.

Q. Giving you a shot?

A. In a shot. And then intramuscular, which is usually how you take vaccine.

So there's different ways. So it would be in a liquid form. There's different ways you can give it. You can give it by IV. You can give it subcutaneously or intramuscular.

Q. And that's where the anti-TNF antibodies of your invention can all be administered to patients in these ways?

A. Absolutely. Absolutely.

Q. Okay. A little bit further down, could you look at the bottom of Column 42?

It's an example -- it's Example Roman Number I. It continues over to the next column then. And just tell us what that example is, that Example No. I.

A. This example describes how the original A2 antibody was produced by Dr. Le and Dr. Vilcek.

Q. Okay. And could you look at examples, Roman Numeral III through Roman Numeral IX at Columns 44 to 48?

What are these?

A. These describe in great detail the steps that we took to find the mouse variable regions from the A2 antibody doing all the recombinant DNA and the cloning that I described to you earlier to finally make the antibody cA2, which has the variable region and then a human constant region attached to it.

Q. Okay. Dr. Ghrayeb, we've heard an awful lot of talk about human antibodies.

Did you provide an example in your patent of making a human antibody, an actual example of the lab work for making a human antibody?

A. We did not describe -- the work that we did, is that your question?

Q. Is there an example in your patent, just like Examples III to IX that we just looked at, you said were the examples that showed how you made the chimeric antibody.

Do you have examples in here about actually making a human antibody?

A. No.

Q. Why not?

A. Because we -- it was never our intention to make a human antibody.

Q. It was not your intention to make a human

antibody, but you said in the summary of your invention that your invention included human antibodies.

A. I think the important thing to understand is that, you know, we were trying to make a very effective antibody that would block the effects of TNF. And we were -- our objective was to try and get that in the clinic as quickly as possible. So we did not deem it necessary to make a human antibody.

However, all the techniques that we described can be used to make a construct using a human variable region just as well as a mouse variable region.

Q. I want to make sure the jury understands. You said it wasn't your intention to make a human antibody.

Are you referring to what you were doing in the lab then?

A. Yes.

Q. Or are you saying that that was not part of your invention?

A. No, I'm not saying that.

Q. So maybe you could explain that a little bit better --

A. I'm just saying --

Q. -- because I think they may be left with the impression that you don't intend.

A. Right.

In the lab, you know, when we were starting to develop the antibody, we were focused on getting a drug on the market. And we could have made it in different ways.

We decided to make it as a mouse antibody attached to a constant. It doesn't mean we could not have made a human antibody or, you know, didn't want to make a human antibody. It's just we decided that it was sufficient to, based on our experience, to make a chimeric antibody.

But anybody who's experienced would realize that that variable region that we cloned from a mouse could easily have been found in a human, so you could make it.

Q. Now, you did come to work on a project for making a human TNF antibody at a later date, correct?

A. Yes, correct.

Q. And that's the product that was just introduced, Simponi?

A. Yes.

Q. And you had something to do with bringing that product to market, correct?

A. Yes.

Q. Now, I'm not sure if you were in the courtroom when this was stated, if it was an argument or

testimony, but the work to discover the antibody for Simponi began in 1997, right?

A. That's about right.

Q. Well, why did you wait until 1997 to start that work?

A. As I, you know, said earlier, we made Remicade. It was a very successful product. We did not -- I mean, as a scientist, I didn't feel the need to do that.

Later on, there was, you know, a need to get into sort of different ways to make antibodies. So we began to experiment with making -- we brought in a technology that was able to make human antibodies. And one of those we tried to make was an antibody to TNF.

Q. Did the fact that you didn't start a project to make a human antibody until 1997 have anything to do with the resources at the company at the time?

A. Absolutely.

Q. Could you explain that?

A. Yeah. I think what people don't always appreciate is how long it takes to develop an antibody after you invent it and how much money it costs.

So Centocor at the time had to make some priorities. A lot of new clinical trials using Remicade were being sponsored, and the manufacturing was being

ramped up. So the majority of the resources were going into developing the product that's on the market.

And when you prioritize, just like you do your budget at home, especially these days, you have to say I can't afford to do that.

So the product was available. I mean, we did have Remicade. A lot of resources were put on it, and we were working on other projects that also, you know, had to wait.

Q. And I would like to clarify some terminology, if we could, because a lot of people have been talking about development of an antibody.

Do you distinguish between the discovery of an antibody and the development of a commercial product?

A. Absolutely.

Q. And what is the difference?

A. You know, the discovery of the antibody involves, as I mentioned earlier, deciding, you know, what disease you want to go after, what target you're going to look for, and then actually physically making the drug; in this case, an antibody.

So you can do all that discovery. You can have that drug available in your hand, but then the rest of it, taking that drug, testing it for safety, spending the money to build another factory to make it, doing all

these large clinical trials to get it to approval, that is development. That could take a really long time. So as a scientist, you're always, you know, making these discoveries, but you don't -- you can't always, you know, push them into the clinic as fast as you would like, because, again, the company has many other priorities and you have a lot of time to wait in line for resources to continue with a development.

So the discovery could be -- could take -- could be very quick. The development, when it's actually getting on the market, could be long, depending when you start, how quickly you go, how much money you're willing to spend, any issues you find along the way that you have to solve. So sometimes it takes a long time.

Q. Now, in the project to develop Simponi, once you started that in 1997, about how long did it take until you had actually discovered the antibody of Simponi?

A. I would say about a year or so.

Q. So you had the antibody within a year after you started the projects?

A. I believe so.

Q. And all the rest of that time, why did it take so long to get it to market?

A. I think in any company, you know, that's a corporate business decision, to take a product into the -- to spend the resources to take it into the clinic.

Q. And what was done during all those years before it was brought -- what had to be done before it could be brought to market?

A. I think -- so once you get the go-ahead, you know, you have to find out how to make it efficiently and, of course, effectively. You had to test it in animals. You had to work on it in the lab as well as in different models to see that, you know, that's the product you want.

And then you start very slowly, you know, giving it to patients. You know, small numbers first, small doses increased to look at the safety. And then you increase the -- you start developing then. If it's successful in the early stage and is safe, you then give it to more patients. And then finally, you do a very large clinical trial with a lot of patients to prove to the FDA that you have a drug that is effective.

So that's a long process.

And in the case of Simponi, what we decided to do was to go after three different indications at the same time. You saw earlier this morning, it talks about

when the drug was approved for Crohn's disease, when it was approved for RA and other diseases.

In the case of Simponi, we decided to go for more than one indication at the same time. So that involved many more trials, a lot more expense and time.

Q. And so all the hundreds of millions of dollars that it costs to bring Simponi to market, was an awful lot of that doing the clinical trials, doing the patient testing?

A. I would say the majority of it was that.

Q. Now, before I go to the last couple of examples in your patent I want to talk about, I just want to go back to one, revisit one issue.

We looked at some disclosure that you said was added to your patent in February of '94, Dr. Marks' article on phage display, the reference to human variable regions, a discussion of some affinity maturation techniques that you said were added in February of '94.

Does that refresh your recollection that this reference to human antibody in the Summary of Invention was also added in February of 1994?

A. I believe so, yes.

Q. Okay. Let's look at Example 21, please, at Column 6 -- I'm sorry -- Example 20 -- beg your

pardon -- at Column 59.

I'm getting ahead of myself.

What is described in Example 20?

A. Example 20 describes the first time we actually gave the antibody cA to patients suffering from rheumatoid arthritis.

Now, this -- when you first try a new drug, you usually give it to the patients who are, you know, most advanced and have, you know, failed a lot of treatments. The idea is that, you know, if there are any issues, at least those patients can benefit from them, and, you know, you try it on the most difficult group of patients first.

So this was a study that was done in England where patients were treated with Remicade over a two-week period with the dose that is mentioned there. And then a second group was treated with, you know, a lower dose.

What happens after the patients were treated is within 48 hours a lot of them were starting to feel the effects of the antibody. And I was fortunate enough to actually visit the hospital in England when they were -- the patients were being treated, and I met some of them.

And to me, it was like the most humbling

experience, because they were starting to tell me how well they felt after taking this one dose of this antibody, how one of them was a psychologist who hadn't worked in two years and then was now able to go back to work.

So for me, I just began to appreciate how important this drug is, how important, you know, my work is. So it was a great experience. And it also showed us that we really chose, you know, the right drug. You know, we spent the time; we chose a drug that was incredibly effective.

Q. And if you could look at Column 21, please. That's Example 21, starting at Column 67.

And tell us what's described there.

A. Okay. So this describes the treatment of a patient who suffered from Crohn's disease also with cA2. So this researcher in Holland -- his name is Dr. Van Deventer, who was working with us on another project, and he is an expert on Crohn's disease.

Now, Crohn's disease, as you can see here, is a very debilitating disease. It's very difficult. I happen to know, because my sister has it.

And what this girl was facing is after all these treatments that didn't work, the inflammation was so bad that they were going to remove part of her

intestine or colon. When Dr. Van Deventer was at Centocor and he saw -- you know, he met Dr. Feldmann and he saw the data that I described to you earlier.

And he had always a theory that TNF was also involved in Crohn's disease. So he wanted to test it. And there's a process that where the FDA allows you to supply, you know, one dose of drug for compassionate use for a case where, you know, it's kind of either life or death or something like this, or face surgery for a very young child.

So the dose was sent to the Dr. Van Deventer. He administered, and very quickly this patient started the symptoms that you mentioned there. Diarrhea, pain and so on went away. The inflammation was under control, and there was no need for her to have surgery. In fact, she started to eat.

That's a big thing about people with Crohn's disease is, you know, they have to choose what type of food. It's really a very, very difficult disease. So this patient recovered. And, again, we had yet another proof of how effective this drug would be.

Q. What was your reaction to learning of these clinical results?

A. You know, as I said before -- I mean, you try to be humble, but in those cases, you just think about,

you know, what you achieved and how important your work is.

Q. Thank you very much, Dr. Ghrayeb.

THE COURT: Cross-examination --

MR. LEE: Yes, Your Honor.

THE COURT: -- Mr. Lee?

MR. LEE: May I proceed, Your Honor?

CROSS-EXAMINATION

BY MR. LEE:

Q. Good afternoon, Dr. Ghrayeb.

I started a chronology. I started to try to write a little bit more clearly.

So that the jury can understand the chronology, you said that in February of 1994 there was a patent application filed, correct?

Is that right?

A. Correct.

Q. And that's the patent that you've just -- patent application that you've just been discussing with Ms. Elderkin, correct?

A. Correct.

THE COURT: Counsel, y'all need to approach just a minute.

A. This was filed --

THE COURT: Wait just a minute. I need

to talk to the lawyers.

(Bench conference.)

THE COURT: Is this your associate that's sitting right here across from Mr. Beck?

MR. LEE: Yeah, I think it is.

THE COURT: Okay. When she doesn't like something the witness says, she rolls her eyes, does these expressions. She's got to stop that.

MR. LEE: Okay.

THE COURT: I mean, I think she's doing it subconsciously.

MR. LEE: I'll take care of it.

THE COURT: I know you will. I just don't want it to get out of hand.

(Bench conference concluded.)

MR. LEE: May I proceed, Your Honor?

THE COURT: Yes, please do.

Q. (By Mr. Lee) So February 1994 is the patent application that you discussed with Ms. Elderkin, correct?

Is that right?

A. Yeah. It's a continuation of that.

Q. Now, before February of 1994, as you told us, the scientists at NYU, Dr. Le, Dr. Knight, had made A2, correct?

A. Dr. Le and Dr. Vilcek, yes.

Q. Right. And Dr. Le and Dr. Vilcek had made A2 in 1990, correct?

A. That's about right, I think.

Q. So if we put 1990.

Now, A2 is a mouse antibody, correct?

A. Correct.

Q. And this is a Centocor mouse antibody, right?

A. Yes, sir.

Q. For NYU?

A. Yes, that's right.

Q. Let's put here NYU/Centocor.

Now, you know in 1986 Dr. Moller had made a mouse antibody to TNF-alpha, correct?

A. I don't recall.

Q. You know it was done before 1990, don't you?

A. There were other antibodies disclosed before 1990, I believe. Mouse antibodies.

Q. My question is very specific: Did Dr. Moller describe a mouse antibody to TNF-alpha before 1990?

MS. ELDERKIN: Your Honor, can we approach?

(Bench conference.)

MS. ELDERKIN: This is not a prior invention story. These claims do not cover mouse

antibodies, who did what, when, where.

THE COURT: You have gone into the history of all this, ma'am. You've gone into this. I don't know what we're going to do about argument, but you developed this history, and he's entitled to cross-examine the witness.

Now, where are you headed there, Mr. Lee?

MR. LEE: I just want to get the date, and I'm going to move right back --

THE COURT: Well, okay. I think he's --

MS. ELDERKIN: It seems to me like it's a prior invention defense, even if your opening argument --

THE COURT: Well, I ruled on that, and I didn't see anything inappropriate in opening argument, okay?

You still haven't gotten your young woman's attention now. I'm going to get her attention in a minute.

MR. LEE: I got it.

THE COURT: You got it? I'm telling you that she's still doing this -- oh, like --

MR. LEE: I told her to look at the screen.

THE COURT: Well, just -- she's going to

have to learn, if you're sitting in trial in a federal courthouse, you can't argue your case to the jury through your facial expressions. It can get rough.

(Bench conference concluded.)

Q. (By Mr. Lee) Okay. Do you have my question in mind?

A. Yes.

Q. Before 1990, when Centocor and NYU had A2, had someone else not associated with Centocor, not associated with NYU, come up with a mouse antibody to TNF-alpha?

A. If you look at the patent, it has several references to --

THE COURT: Doctor, that's not what his question was. Listen to what his question is.

THE WITNESS: Okay. I'm not sure what --

THE COURT: Okay. Let me finish, okay?

THE WITNESS: Yes, sir.

THE COURT: You listen to what his question is and answer that question. If you don't understand his question, just tell him you don't understand it. And don't try to add to something, because your counsel will have the opportunity to ask you additional type questions, okay?

Let's move along.

Q. (By Mr. Lee) I'll restate the question, Dr. Ghrayeb.

Isn't it true that before Centocor and NYU isolated or made a mouse antibody, other people in other laboratories had already done it?

A. Yes.

Q. And isn't it true that Dr. Moller was one of them, and he did it around 1986?

A. I know Dr. Moller is one of the references we cited in the patent, but I don't remember when he actually made it.

Q. But you remember that it was before 1990?

A. Yes.

Q. So we'll just write before 1990.

Now, would you tell the jury -- Dr. Moller is associated with Abbott, is he not?

A. I really don't know.

Q. You don't know one way or another?

A. No.

Q. But what you do know is he made a mouse antibody?

A. Yes.

Q. Now, let's skip up to 1997. That's when you told us the project that led to Simponi starting, correct?

A. Correct.
Q. I'm just going to write Simponi project. And I think you told us it took about a year to make it.
A. That's my recollection. It could be plus or minus. I can't remember exactly.
Q. Let's take your best recollection.
So in 1998, you had made Simponi, correct?
A. Correct.
Q. And isn't it true that 1998 is the first time that you had a high-affinity neutralizing fully human antibody to TNF-alpha?
That's the very first time, correct?
A. Yes.
Q. Now, you sought a patent on Simponi, correct?
A. I am not an inventor on that patent. I don't know all the details.
Q. Well, you were the supervisor for the project, correct?
A. Correct.
Q. And when you sought the patent for Simponi, didn't you tell the Patent Office what you had or what Centocor had was a fully human antibody?
A. I would have to see the patent.
Q. Have you seen the patent before?
A. No.

Q. So you've never seen the patent that Centocor has that covers Simponi?

A. Let me rephrase.

I mean, in all those years -- we're talking ten years ago -- I've seen -- I'm sure I've seen a copy of it, but I don't recollect, because it wasn't something that I read every word, every line. I knew it was filed.

Q. Okay. Well, let me --

MR. LEE: This is this evidence, Your Honor.

Q. (By Mr. Lee) Let me bring up DX27 on the screen. And let's look at the front page first, and let's look at the date when this patent issued. This is Centocor's patent that describes Simponi, correct?

And it's in your notebook, so you can look at the whole --

A. Which number? I'm sorry.

Q. If you look at Tab 6, Dr. Ghrayeb.

A. Thank you.

Q. -- you'll find the full patent, and we're just going to put the front page on the screen so the jurors can see it and you can see it.

But you look at whatever is easiest for you.

A. Yes.

Q. This is the patent that issued in July 31, 2007 that covers Simponi, correct?

A. Right.

Q. And it was applied for on August 1, 2001. Do you see that?

A. Yes.

Q. And I notice in the related U.S. application dated -- do you see this where I'm pointing?

A. Yes.

Q. There are just a couple of other applications there, aren't there?

A. Okay. I see it.

Q. Now, let me show you Column 54, Line 11. And you can look at it on the screen, or you can look at it on -- in the hard copy, whichever is easier. Actually, let's go to Column -- I'm sorry -- Column 50, Line 36, and I'm going to highlight the sentence that begins at Line 36: The unexpectedly high affinity of these fully human monoclonal antibodies make them suitable candidates for therapeutic applications in TNF-related diseases, pathologies, or disorders.

Did I read that correctly?

A. You read it correctly.

Q. So in 2001, Abbott filed -- Centocor files a

patent application, right?

Is that right?

A. Are you telling me that --

Q. I'm asking you; isn't that true?

A. You know, I -- I have not followed, you know, the -- but -- I mean, it's got to be true, if you're telling me that.

Q. Well, it's on the cover of the patent. Do you have the patent?

A. The first --

Q. The very first page, it says: Filed, August 1, 2001, correct?

A. Correct.

Q. And when you filed for this application in 2001, what you told the Patent Office is that the unexpectedly high affinity of these fully human monoclonal antibodies, that's the phrase that was used, correct?

A. That's -- that's what it says.

Q. Right. So this project that you were in charge of, that started in 1997, that produced Simponi, produced a patent that used the words fully human monoclonal antibodies, correct?

A. Correct.

Q. And it's true, is it not, that until 1998,

Centocor had never developed -- strike that.

Before 1998, Centocor had never made a fully human monoclonal antibody to TNF, correct?

A. It's accurate to say we've never attempted to make a fully human antibody to TNF.

Q. Now, let's go back to your patent. Ms. Elderkin asked you for some -- asked you some questions about the patents itself.

Let me bring up the first page of the '775 patent. And the full patent, Dr. Ghrayeb, is in the notebook before you at Tab 2. Again, you use whatever is best for you.

Do you have your patent before you?

A. Yes.

Q. Now, as you pointed out, on the first page, there is a long list of prior applications, correct?

A. Related to the patent, yes.

Q. Now, let me go to Column 1 of your patent. And when I say your patent, there were several other inventors, correct?

A. I'm not sure what -- what you're asking me.

Q. There were several other people who are identified as inventors of the '775 patent, correct?

A. Yes. I went through that, yeah.

Q. Now, turn in the patent to Column 1. I'm

going to highlight it, but I just want to focus you on the last portion of the first paragraph. It begins about Line 26.

Do you see the sentence that says: Each of the above applications are entirely incorporated by reference herein? Do you see that?

A. I see that.

Q. One of the applications was filed in 1991, correct?

A. Yes, that's listed there.

Q. Right.

All right. So let's look at what the 1991 app -- you understand when you incorporate something by reference, it means it's as if I set it forth in writing here, correct?

A. I -- I'm not understanding. I mean, I'm assuming that that's right, since you're telling me.

Q. All right. Let's turn, if we could, to the 1991 application that's incorporated by reference. And at Tab 3, you'll find DX25.

MR. LEE: Which is in evidence, Your Honor.

Q. (By Mr. Lee) Do you have that before you?

A. Yes, I do.

Q. This is the March 1991 application, correct?

A. Correct.
Q. You've seen this before, have you not?
A. Yes, I have.
Q. And this is the application that -- one of the applications you filed with the Patent Office, correct?
A. Correct.
Q. Now, let's see what you said to the Patent Office about this issue of whether having some portion that is mouse makes a difference.
In fact, you told the Patent Office back in 1991 that there were problems with an antibody that was all mouse, correct?
A. I would assume so, yes.
Q. Right. So let's turn, if we could, to Page 8 of the application.
MR. LEE: And could I have the bottom paragraph blown up?
Q. (By Mr. Lee) Now, you have in mind that this is what you said to the Patent Office about the difference between mouse, chimeric, and human, correct?
A. Correct.
Q. And you start by talking about monoclonal antibodies, correct?
A. Yes.
Q. And you say that monoclonal antibody

technology has spawned a revolution in biology equal in impact to that of a recombinant DNA technology.

And then you refer to mABs. Do you see that?

A. Yes.

Q. MABs, so the jury knows, is mouse antibodies, correct?

A. No.

Q. What is it?

A. It's monoclonal antibodies.

Q. All right. And the only ones that you had had so far were either mouse or chimeric, correct?

A. At the time?

Q. Yes.

A. Yes.

Q. So in 1991 --

A. If compared to TNF?

Q. In 1991, the TNF were related to mouse and chimeric.

And so you go on to say, Their success, referring to these antibodies, in the treatment of human diseases, including microbial infections, autoimmune disease, and cancer, has yet to be established.

Despite their exquisite specificity, mouse ABs, by their very nature, have limitations in their applicability to human medicine.

Did I read that correctly?

A. Yes.

Q. Now, in that sentence, when you say mouse ABs, you're referring to a mouse antibody, are you not?

A. I'm referring -- I'm referring to a mouse monoclonal antibody.

Q. Fair enough.

And what you say is, by their nature, those mouse antibodies have limitations when you apply them to human medicine, correct?

A. That's what I'm saying.

Q. And then you go on to say, most obviously, due to their murine origin, they are foreign proteins in humans, induce anti-murine immune responses and tend to be cleared more rapidly from the circulation, correct?

A. Correct.

Q. So when you wanted to get the patent from the Patent Office, you explicitly described to them the problems with a mouse antibody, correct?

A. That's part of the introduction to the facts at the time.

Q. Right. At the time that you were seeking your patent, correct?

A. At the time that this was written, yes.

Q. Right. And it was incorporated into this 1994

application by reference as we saw, correct?

A. Yes.

Q. All right.

MR. LEE: Now, let's go to the next page. And on the next page, I would like to blow up the full paragraph, if we can.

Q. (By Mr. Lee) And again, you can use the hard copy or the screen, whichever is easier for you.

You then state to the Patent Office, The development of human monoclonal antibodies could circumvent the above problems. Strike that. I'm sorry.

It says, The development of human mABs that could circumvent the above problems has encountered a number of obstacles, correct?

A. Correct.

Q. That's what you say in your application, correct?

A. Correct.

Q. And then if we go through the rest of this paragraph, you identify three different barriers to developing a human monoclonal antibody, correct?

A. I'm just, you know, reading.

Q. Sure.

A. I think so, yes.

Q. All right. One of the problems was that the

method described to do it involved a virus, and it didn't seem like such a good idea to have a method that used a virus, correct?

A. That's -- that's not the reason why it's difficult.

Q. Well, EBV refers to something that involves a virus, correct?

A. That -- that's correct.

Q. All right. And let me see if I can just get through this quickly.

The three reasons were, there was no way to make it commercially practical; you had to use this Epstein Barr Virus; and there are just problems in making human antibodies to human proteins.

That's, in general, what the paragraph says and what you told the Patent Office, correct?

A. In general, yes.

Q. And in your application, the one that Ms. Elderkin went through, you don't describe any solution to these problems, do you?

A. Not to my knowledge, no.

Q. Right. So back in 1994, what you do say about a fully human monoclonal antibody is, there are lots of problems -- or there are some problems, and you don't describe a solution, correct?

A. A solution that, you know, has been shown to be predictable in solving that problem.

Q. Right. Now, you said that you might have told people how to do it, and you referred to an article on phage display --

A. That's correct.

Q. -- is that correct?

And you said that your patent mentioned this article on phage display.

MR. LEE: Could I have the article brought up on the screen, which is DX381?

Also in evidence, Your Honor, and it's Tab A.

Q. (By Mr. Lee) Now, Dr. Ghrayeb, this article was by someone named Dr. John Marks? Jim Marks. I'm sorry.

A. It's not -- I don't think it's John.

Q. And Dr. Marks is actually Abbott's expert in this case, isn't he?

A. That's what I hear.

Q. Yeah. He's one of the pioneers of phage display technology, correct?

A. Correct.

Q. Now, you told the jury just a few months ago -- few minutes ago that you mentioned this concept

of phage display and that it could be used to make a fully human monoclonal antibody, correct?

A. Correct.

Q. Now, the truth of the matter is, no one at Centocor has ever used phage display to make a fully human monoclonal antibody to TNF; isn't that true?

A. Nobody has ever attempted to use phage display to make a human antibody for TNF.

Q. Right. So the very thing that you told the jury your patent taught someone to do if you want a fully human antibody, Centocor has never done, correct?

A. We have not done it, but Dr. Marks has.

Q. Right.

A. You know -- I mean, he's shown that there is a technique you could use to make it.

Q. So the one thing you would agree about in terms of who could do what in 1994, Dr. Marks probably knows better than anybody, correct?

A. That I disagree.

Q. All right.

A. I mean --

Q. Well, let me ask you this: When you started your project in 1997, did you just go use a phage display that you taught the world about in 1994?

A. We considered it --

Q. Did you do --

A. -- seriously.

Q. Did you do it?

A. We did not.

Q. Right. In fact, when you started in 1997, you used something called transgenic mice, correct?

A. That's correct.

Q. And isn't it true, in your entire 1994 application, there is no mention of transgenic mice?

A. That's correct.

Q. So the method that you used when you went to develop a fully human antibody is one that's not even mentioned in your own patent, correct?

A. Correct.

Q. All right. Now, let's talk about the work that Centocor did do before 1994 with fully human antibodies.

First, you told me that Cyntoxin was a fully human antibody, correct?

A. Correct.

Q. And it was unsuccessful for a variety of reasons, but in any event, it never became a product on the market, correct?

A. Correct.

Q. But it was fully human, correct?

A. Correct.

Q. Now, you also had some experience with another fully human antibody called 7.T.1, correct?

A. You would have to jog my memory about that one.

Q. Isn't it true that in 1989, Centocor received a human antibody called 7.T.1?

A. I won't dispute that. I didn't receive it, but I won't dispute that.

Q. Well, let me bring up DX140, if I could. Do you have DX140 on the screen?

A. Can you tell me what tab number that is?

Q. Sure. DX140 is a Tab 4. I want you to tell me when you've got it there.

A. Okay.

MS. ELDERKIN: Objection. I believe that exhibit is not admitted.

MR. LEE: I have it's preadmitted. Well, then don't put it on the screen.

Q. (By Mr. Lee) Let me ask you this, and I'll lay the foundation.

Do you have Exhibit 140 before you?

A. Yes, I do.

Q. This is a letter on Centocor letterhead, correct?

A. Correct.
Q. And it is to Michael K. Hoffmann, correct?
A. Correct.
Q. From Hubert Schoemaker, correct?
A. Yes.
Q. And it's dated June 21, 1989, correct?
A. Correct.
Q. And you recognize Dr. Schoemaker, he was the Chairman of the Board at Centocor, correct?
A. Yes.
MR. LEE: We offer it, Your Honor.
THE COURT: Well, y'all approach. You've got all this handwriting nobody has talked to me about yet.
(Bench conference.)
THE COURT: It's Centocor's statement. Why is it not admissible?
MS. ELDERKIN: It's not on the preadmitted list. I don't know what --
THE COURT: Well --
MS. ELDERKIN: -- if it was --
THE COURT: -- what is all this handwriting you see?
MR. LEE: That's just what was produced to us, Your Honor. We just need this portion with the

statement, and then there's a letter.

MS. ELDERKIN: There's also no evidence that this witness has ever seen this document or knows anything about it.

THE COURT: Overrule the objection. He's testified who this guy is.

Are you disputing the authenticity of something y'all produced? I overrule that. It shows that y'all produced it.

MS. ELDERKIN: We did produce it, Your Honor. I don't know what the handwriting -- whose handwriting it is.

THE COURT: All right. Well, it's admitted.

(Bench conference concluded.)

THE COURT: All right. That exhibit is admitted into evidence.

Q. (By Mr. Lee) This is a letter that's dated June 25th, 1989, correct?

A. June 21st.

Q. June 21st, 1989.

And this is from Centocor, right?

And the Chairman of the Board says, We are very interested in human anti-TNF mABs, correct?

A. As per the letter, which I -- we don't have in

front of us. So I don't know what would be in it.

Q. Well, let's now turn, if you would, to Exhibit -- Defendant's Exhibit 142, which is also in evidence. This is from Jan Vilcek. He's one of your co-inventors, correct?

A. Correct.

Q. He's at NYU, correct?

A. Correct.

Q. And you know who Jimmy Le is. That's Dr. Le, correct?

A. Yes.

Q. Also one of your co-inventors, correct?

A. Correct.

Q. And what happened in 1989 is, Centocor got a fully human monoclonal antibody to TNF, and it didn't work, and you couldn't make it work, correct?

A. It -- what you can say is that this antibody is just not -- wasn't good enough to satisfy our needs.

Q. Well, Dr. Ghrayeb, the letter says, quote, The results indicate that 7.T.1 has virtually no neutralizing activity even at high concentrations, correct?

A. Right.

Q. No neutralizing activity means it doesn't work, correct?

A. That particular antibody didn't work, correct.
Q. Right. So what we do know is, before 1994, Centocor had actually explored one human monoclonal antibody, and it didn't work, correct?
A. Correct.
Q. And it also had a fully human monoclonal antibody product called Cyntoxin that didn't make it to market for a variety of reasons, correct?
A. Two different, you know, reasons for not working.
Q. Right. But neither worked, correct?
A. Neither -- neither of them was approved.
Q. Right. And that was it. That was it for Centocor until 1997 for fully human monoclonal antibodies, correct?
A. That was for looking for any antibodies to TNF.
Q. Right. Now, just a couple more questions. When you went through all of the patent specification with Ms. Elderkin and we talked about the different portions, you mentioned B-cells at one point, correct?
A. I may have, yes.
Q. Now, Centocor never tried to use B-cells to produce a fully human monoclonal antibody, correct?
A. There was a group at Centocor, which was

working at that time.

Q. And they were unsuccessful, correct?

A. No. They produced human antibodies.

Q. Fully human monoclonal antibodies that were high affinity and neutralizing?

A. They were antibodies that would be, you know, similar or better than Cyntoxin. So there was a program to do that, and this whole approach was tried.

Q. Did you try to use B-cells to produce fully human monoclonal antibodies to TNF-alpha?

A. No, we did not.

Q. Did you try to use phage display to produce fully human monoclonal antibodies to TNF-alpha?

A. We did not even consider it.

Q. Did you try to use any of the different techniques that you've described to Ms. Elderkin to produce a fully human monoclonal antibody to TNF-alpha, sir?

A. We did not.

Q. No, you didn't.

MR. LEE: Nothing further, Your Honor.

THE COURT: Ms. Elderkin?

MS. ELDERKIN: Okay. Thank you.

REDIRECT EXAMINATION

BY MS. ELDERKIN:

Q. Dr. Ghrayeb, Mr. Lee asked you some questions about the 1991 application, and I think it was characterized as statements about barriers to making human antibodies.

But in your 1994 application, what did you add with respect to making human antibodies?

A. We added, you know, information about how you could make human antibodies and that it would be possible to do that, to make antibodies to human TNF.

Q. Okay. Now, is it necessary -- you have experience with a number of patents.

Is it necessary in your patent to disclose every possible method for making the antibodies of your invention?

A. No.

Q. Did the fact that Cyntoxin didn't get approval have anything to do with the fact that it was a human antibody?

A. Not at all. As I mentioned earlier, a mouse antibody also failed in clinical trial.

Q. There are lots of antibodies that don't bind to TNF well enough to do anything, right?

A. Exactly.

Q. Did the fact that -- and 7.T.1, was that an anti-TNF antibody?

A. Based on, you know, the -- the -- this letter that I saw, it must have been.

Q. It must have been. Okay.

A. But --

Q. I'm sorry.

A. Let me just explain, and I explained this a little earlier.

When you are looking for the right antibody, you'll get ones that don't work, and you'll throw them out.

So this was one of those antibodies that, you know, was produced and just was clearly not effective. So we threw it out.

I mean, we were not interested in an antibody that didn't work. It isn't even necessary to try and improve it, because it had like zero activity. So we just moved on to, you know, the antibody that would work.

Q. And did the fact that the 7.T.1 antibody didn't work have -- was that because it was a human antibody?

A. Absolutely not.

Q. There are a lot of antibodies that could bind TNF but weren't good enough to ever be made into a therapeutic drug that could be used in patients, right?

A. I would agree with that.

Q. And you found the ones that were good enough, correct?

A. Correct.

Q. And the ones that have special binding characteristics like A2?

A. Correct.

MS. ELDERKIN: Thank you, Dr. Ghrayeb.

MR. LEE: Nothing further, Your Honor.

THE COURT: All right. You may step down.

MR. SAYLES: May it please the Court.

At this time, we'd call Dr. Robert Kamen by deposition, and I have a stipulation of the parties I would like to read in advance of playing.

THE COURT: Okay.

MR. SAYLES: Dr. Ghrayeb might be called in rebuttal. May he stay in the courtroom, or will he still be subject to the Rule?

THE COURT: Still subject to the Rule.

MR. SAYLES: All right.

THE COURT: And just so counsel knows, you know, unless I expressly excuse someone from the Rule, it still applies to them.

MR. SAYLES: All right, sir.

This is an introduction to Dr. Robert Kamen, as agreed by the parties in the introduction.

Dr. Kamen has an undergraduate degree in biophysics from Amherst College and received his Ph.D. in molecular biology and biochemistry from Harvard University in 1970.

Beginning in 1991, Dr. Kamen was the President of BASF. Dr. Kamen oversaw the development of the Humira product.

(Video playing.)

QUESTION: Good afternoon.

Before the break, we were talking about Plaintiff's Exhibit 185, Dan Tracey's report on a symposium that he had attended and learned about Centocor's chimeric antibody.

Do you recall that?

ANSWER: Yes.

QUESTION: Did this work by Centocor on cA2 have any influence on BBC with respect to whether it would continue to develop its own anti-TNF-alpha antibody?

ANSWER: The exhibit talks about work done by Marc Feldmann and Maini. I guess there are Centocor authors on it. I've always thought of this as the Feldmann work, not the Centocor work at this point.

I think the answer to your question is -- no. Now I've forgotten your question. Please repeat it.

QUESTION: Okay. Did the work by Feldmann on the Centocor antibody cA2 influence BBC's decision to proceed with the development of its own anti-TNF-alpha antibody?

ANSWER: At the time that we became aware of this, we were already working on a project to make a fully human anti-TNF antibody. We had a list of potential indications, and this was exciting and pointing us toward an indication which appeared to have some clinical verification.

QUESTION: So did the work by Feldmann on Centocor's cA2 antibody influence BBC's decision to proceed with the development of an anti-TNF-alpha antibody for an RA indication?

MS. WIGMORE: Objection to form.

ANSWER: As far as I know, this was the first public disclosure of the efficacy of an anti-TNF on RA that had an impact.

QUESTION: Can you look back at Plaintiff's Exhibit 182, your deposition transcript?

ANSWER: Yes.

QUESTION: At Page 90 of the transcript, starting at Line 22, you were asked at this deposition:

"So did the work by Centocor on Remicade on cA2 influence Abbott's decision to proceed with the development of what became Humira?

And you answered, Yes, it did.

ANSWER: Uh-huh. Yes, I see that.

QUESTION: Is that -- were those statements -- was that statement true at the time?

ANSWER: Yes.

QUESTION: And how did the work by Feldmann on the cA2 antibody impact BBC's decision to proceed with its own TNF-alpha antibody?

ANSWER: It made us think hard of RA being an indication for the antibody which we were making. And we proceeded to, you know, learn more about rheumatoid arthritis and proceeded down that thought pattern.

QUESTION: Do you recall answering questions from Ms. Verrecchio about antibody libraries, phage display, and guided selection?

ANSWER: Yes.

QUESTION: And do you recall testifying that those technologies were used by BBC and CAT in the development of D2E7?

ANSWER: Yes. Could you repeat which -- which three technologies?

QUESTION: Sure. Were the antibody library technology, the phage display technology, and the guided selection technology together, in and of themselves, enough for BBC to develop D2E7?

ANSWER: No, they were not.

QUESTION: What, if any, additional work was needed?

ANSWER: The hardest part of a hard project was the affinity maturation, which took a very considerable proportion of the three-year time period. And in the course of that work, we developed some approaches which were not previously known to CAT.

QUESTION: And can you give us some examples?

ANSWER: Well, the key was, the hope of phage display, which, in my experience, has proved to be incorrect, was that one could always select out an improved version of an antibody from a population of less desirable antibodies; in particular, that you could mutate some sequences, keep a big pool, and do some sort of selection amongst millions of phage to pull out one of higher affinity.

That, in fact, turned out not to work on this project and other projects in that once one had candidates of moderate affinity but still less affinity

than needed for a clinical candidate, you could no longer do selections, because you always got the parental version back.

So we had to switch into a mode of not selecting but doing versions of medium throughput screening. We had to look one by one individually and assess the properties of phage, which is very laborious. And to simplify that, we started to do what was called off-rate selections in which we tried to enrich libraries for variants which formed more stable complexes with TNF, and then we took significant numbers of candidates and then individually analyzed their off-rates by biophysical methods.

And that was an extremely laborious process that took some time, and it really had not been at all anticipated by the technologies that you're talking about.

QUESTION: Approximately how much time did it take from the time that BBC decided to pursue a fully human antibody to TNF and the time that D2E7 was created?

ANSWER: Well, I believe that D2E7 was created in early 1995, and the project was started, shall we say, beginning in '92, late '91. So that's three years?

(End of video clip.)

THE COURT: Is there any other portions of this deposition?

MR. SAYLES: Nothing from the Plaintiff. He played it all the way through, I believe.

MR. BECK: Nothing from us, Your Honor.

THE COURT: And was all of that time charged to the Plaintiff? Or we'll talk about it during a break.

MR. SAYLES: We'll give you the division --

THE COURT: Okay.

MR. SAYLES: -- on that.

THE COURT: Who will be your next witness?

MS. MULLIN: May it please the Court, Your Honor.

Plaintiff's call Susan Tam.

While Ms. Tam comes, may we approach the bench for a moment, Your Honor?

THE COURT: Yes.

(Bench conference.)

THE COURT: Okay. What's up?

MS. MULLIN: Ms. Tam did some testing for the litigation. We have her laboratory notebook with

us. It was not preadmitted by Judge Everingham. He indicated that it was not admissible under 803.6, and we agree, but I would like an opportunity to lay foundation to admit it under 803.1, which is really the appropriate rule for it.

THE COURT: Well, you can lay the found -- you can ask the questions and move for its admission.

MS. MULLIN: That's what I wanted to do, but when I brought it up with your clerk this morning, he suggested that before I even hand the notebook to her that I make sure I get permission from you since it was not preadmitted.

THE COURT: Well, just say this is something I want to put in evidence. I want to ask you some questions about it.

MS. MULLIN: Okay. That's fine. I just --

THE COURT: All right.

MS. MULLIN: I don't want to get in trouble.

THE COURT: You're not going to get in trouble.

MS. MULLIN: Okay. Thank you, Your Honor.

THE COURT: I'm not wanting anybody to get in trouble except him.

MR. BECK: If you get in trouble, we all get in trouble.

(Bench conference concluded.)

COURTROOM DEPUTY: Raise your right hand, please.

(Witness sworn.)

SUSAN TAM, PLAINTIFFS' WITNESS, SWORN

DIRECT EXAMINATION

BY MS. MULLIN:

Q. Could you please state your name for the record.

A. Susan Tam.

Q. And, Ms. Tam, could you please briefly describe your education after high school?

A. I received a bachelor's in biology at UC Berkeley. Then I received a master's in cell biology at U.T. Riverside. And I had -- I was in the Ph.D. program at UCLA for three years, and then my husband, who finished his postdoc, got a job offering on the east coast.

Q. And did you move with him to the east coast at that time?

A. Yes, I moved with him.

Q. Are you currently employed?
A. Yes, I am. I work at Centocor.
Q. How long have you been with Centocor?
A. A little more than 26 years.
Q. And what's your current position there?
A. I am a principal research scientist.
Q. Have you had that position for all 26 years?
A. Yes. I started as an entry-level scientist, and through the years, I've been promoted to various positions of increasing responsibility, but always in research.
Q. Does part of your job involve lab work?
A. Yes. I am primarily a bench scientist.
Q. What does that mean to be a bench scientist?
A. That means I design and perform the experiments.
Q. Okay. What kind of experiments have you done in the course of your normal duties at Centocor?
A. I work with antibodies. My job is to design studies to study the physical properties of antibodies, as well as the functional characterization of the antibodies either on purified proteins or on cell surfaces or on tissues in small animals.
Q. Have you done any testing of antibodies in connection with this case?

A. Yes. I have tested Humira and A2.

Q. Did you make any records while you were doing these tests?

A. Yes. All my testing and results are included and documented in a laboratory notebook.

MS. MULLIN: Permission to approach the witness, Your Honor?

THE COURT: Yes.

Q. (By Ms. Mullin) Ms. Tam, I've handed you a copy of what's been marked as Plaintiffs' Exhibit 854. Do you recognize that?

A. Yes. This is my notebook in which I recorded all my findings.

Q. And what kinds of tests did you do for this case that are recorded in that notebook?

A. I was asked to do a Scatchard analysis on Humira and also to do competition studies or a competition assay.

Q. And the assays that are recorded in your notebook, were they assays that you actually performed?

A. Yes. I have performed all the studies in this notebook.

Q. And were you the one who actually put the entries in the notebook?

A. Yes.

MS. MULLIN: Your Honor, at this time, I move for admission of PX854 under 803.1.

MS. WIGMORE: No objection.

THE COURT: Pardon?

MS. WIGMORE: No objection.

THE COURT: Received.

MS. MULLIN: Thank you.

Q. (By Ms. Mullin) Okay. Now, you've mentioned that you did some testing of --

THE COURT: What's going to be the number of that exhibit for the record?

MS. MULLIN: It's 854, Your Honor, Plaintiffs' Exhibit 854.

THE COURT: 854. Okay. Thank you.

MS. MULLIN: Thank you.

Q. (By Ms. Mullin) Okay. So at the time you did the test -- I think you mentioned affinity and competition test that are recorded in your notebook -- what did you know about the antibodies that you were testing?

A. I knew that one antibody was Humira. That is because we bought it.

The other two antibodies were given a numerical code, the C code given by Centocor.

Q. Did you know what those -- what the C code

antibodies were at the time you did your testing?

A. All I knew was that they were antibodies against TNF.

Q. Do you know now what those antibodies were that you used in your testing?

A. Yes. They are A2.

How I know is that I carefully looked through trace notebooks of the scientists that produced the antibodies from the cell line, and I -- not only did I look through their notebooks, I talked to them personally one on one, as well as their supervisor.

Q. Now, you said they were given C codes in plural. Did you have different samples of A2 that you used in your testing?

A. I had two samples. One was C134A and one was C259A.

Q. And what's the difference, if any, between those?

A. They are both A2.

One was obtained from the ATCC, which is a public depository of cell lines, and the other was -- came from an internal cell bank at Centocor.

Q. At the time that you did your testing, had you ever seen the patent that's involved in this litigation?

A. No, I did not see the patent.

Q. Did anyone suggest to you what they expected the outcome might be or could be or should be in connection with the tests you were doing?

A. No. No one talked to me.

Q. Okay. So then I'd like to talk a little more in detail about the experiments that you did.

The first one you mentioned was an affinity, and I believe you mentioned the word Scatchard. Can you describe very briefly what was the protocol that you used for that?

A. Okay. Very generally, what I did was, I took TNF, and I coded it on a plastic plate. And then I took labeled Humira, and I added it to the plate, incubated it, and then detected the Humira that was bound to the TNF on the plate.

And the Humira is labeled with a radioisotope, so the instrument that detects it is a gamma counter.

Q. And who developed the protocol that you were going to use in your affinity testing?

A. I did. It's standard procedure that I do.

Q. And did you record the results of your affinity test in your notebook --

A. I did.

Q. -- Plaintiffs' Exhibit 854?

A. Yes, I did.

Q. Would you like to look at a page of that notebook?

MS. MULLIN: And if Mr. Ficocello could bring it up on the screen for us.

Q. (By Ms. Mullin) Just very generally, what's reflected on this Page 10?

A. It's not very clear, but this is the printout from the instrument that detects the radioactive Humira that is bound to the plate. So these are the raw numbers as it appears.

Q. And it's actually the machine that counts it and provides you with the data?

A. Yes. And there is a date and -- for the printout.

Q. Okay. I'd like to then turn -- and did you do affinity tests with A2 or just with Humira?

A. Just with Humira.

Q. Okay. And you also mentioned Scatchard. What does that refer to?

A. Scatchard is a method -- it's a mathematical method of analyzing the data. And normally, you display the data as a Scatchard plot.

Q. I'd like to turn then to the other test that you did, the competition assays.

Again, who came up with the protocol for the

competition assays that you did?

A. I came -- I designed the protocol, and I performed the experiments. And again, this is standard procedure for me.

Q. Can you describe very generally what you did for your competition test?

A. Okay. Again, I had coded TNF on a plate, I had labeled Humira, and I also incubated that with unlabeled antibody. In this case, it's unlabeled A2. I would do a series of these experiments with increasing amounts of unlabeled antibody. And the results of -- of these types of tests could be used to determine competition.

Q. Could you turn please to Page 18 of your notebook?

MS. MULLIN: And Mr. Ficocello, if you could bring that up on the screen, please.

Q. (By Ms. Mullin) What's shown on Page 18 of your laboratory notebook?

You do have a pointer, if you can -- I think if you hit the top button.

A. Oh.

Q. There you go.

A. Okay. I always stage my experiments, the purpose, the reagents, my -- the method that I use. And

this is the plate layout or my concentrations. This is the plate.

This -- generally, scientists can follow this type of protocol if they -- if they see it.

Q. Okay. So just going through, the C134A --

MS. MULLIN: I'm sorry, Mr. Ficocello. If you could bring that same piece up, so -- the middle table, so that we can see a little bit bigger.

Thank you.

Q. (By Ms. Mullin) Okay. There's a reference here to C134A. What is that again?

A. That is A2.

Q. Okay. And what is C259A?

A. That is also A2.

Q. Okay. And underneath that, it says Humira.

A. Correct.

Q. And then there's a reference to CNTO -- I want to say 62 --

A. It's 6234. This is a control antibody. It is a -- it is an antibody that does not bind to TNF. And we normally use that to show what the background is. And it's just a negative control --

Q. Okay.

A. -- to verify that everything looks good in the assay.

Q. Can you turn then, please, to Page 19 of your notebook? Again, this is PX or Plaintiff's Exhibit 854.

What's shown on this page, Ms. Tam?

A. This is the raw data for -- this is the -- a printout from the instrument for the competition experiment.

Q. Okay. And so is this data that actually comes out of a machine --

A. Yes.

Q. -- that's doing something?

A. Yes.

Q. And what is the machine doing that's printing out this data?

A. The CPM is counts per minute, and this measures the radioactivity in the well. This is the mount of Humira bound to the TNF.

Q. And how many -- I know we only have a piece of it up, but how many pieces of data do you have?

A. Well, this is a 96-well plate. So for each sample, I would do it in duplicate, and each sample, there is 12 data points or 12 concentrations of the unlabeled antibody.

Q. Did you do the competition assays once or more than once?

A. I did the competition assay twice.

Q. Okay. To start with, is that something different than being in duplicate?

A. Yes. These are two separate experiments. A duplicate is a duplicate sample the same day.

Q. So a duplicate is two simultaneous tests in the same experiment, but you actually did a second set of competition assays?

A. Yes, I did.

Q. Why did you do that?

A. Well, to be accurate.

Now, the first time I did it, I had noticed that in the duplicates, there was one column of numbers that seemed to have like -- it was quite obvious to me -- a pipetting irregularity.

And what a pipette is, it is the device that picks up the volume of sample, and it's a very -- as someone described, it's like a turkey baster. So it's picking up a drop, and there's an -- and if there's an obstruction in the hole, then you're going to get, you know, a different amount pipetted out.

So because the data looked like it was half the value of the duplicate, I just did it again.

Q. Now, you made a reference to a turkey baster. Is the pipette you're talking about the same size as a turkey baster?

A. No. No. A pipette tip measures a very small amount. It's like less than a drop. And the tip of that pipette is like a pencil point, so it's very small. So you can imagine, if you have an air bubble, it can be -- very easily throw off your -- the volume that you distribute.

Q. Is there a standard way that you show this kind of data that's easy to look at?

A. The results for us, we normally display it as a graph.

Q. So if I can interrupt you.

MS. MULLIN: Mr. Ficocello, if you could please bring up Page 26 of Ms. Tam's notebook.

Q. (By Ms. Mullin) And if you look at that. Is this an example of one of the graphs of your competition assay data?

A. Yes.

Q. Okay. And can you just very briefly explain what the points are that are represented on the graph.

A. Okay. This -- the x-axis is the concentration of the unlabeled antibody. And this on the y-axis is the amount of labeled Humira bound or -- yea. And normally, this is a typical curve. This here is the negative control, and that's what we expect.

This curve is computer-generated. It's a

nonlinear fit of the data point. And again, there's 12 data points here. Each data point is a duplicate.

Q. Now, we've heard about C134A and C259A. We know what Humira is. But what are the F105, C7E3, et cetera?

A. Okay. I -- these are just control antibodies that I -- that we sometimes include just to show that there is no competition, because it does not bind to TNF.

Q. Have you ever talked to anyone about the tests you did or just the data that's included in your notebook?

A. No. At the time, I did not talk to anybody. But since then, I have talked to Dr. Greg Adams on all my testing and the results and my findings.

Q. Thank you.

MS. MULLIN: Pass the witness, Your Honor.

THE COURT: All right. We'll take an afternoon break here, Ladies and Gentlemen. Be ready to come back in the courtroom at 3:35, 3:35.

You may leave the courtroom at this time.

COURT SECURITY OFFICER: All rise.

(Jury out.)

THE COURT: Court's in recess until 3:35.

(Recess.)

COURT SECURITY OFFICER: All rise.

(Jury in.)

THE COURT: Please be seated.

All right. Let's continue, please.

CROSS-EXAMINATION

BY MS. WIGMORE:

Q. Good afternoon, Dr. Tam.

Are you aware that this lawsuit was filed in April of 2007?

A. No, I was not.

Q. Now, you described for us some testing that you conducted involving Humira and A2.

When did you conduct that testing?

A. In June of '07.

Q. Thank you.

MS. WIGMORE: I have no further questions.

THE COURT: Okay.

MS. MULLIN: May the witness be excused, Your Honor?

THE COURT: Yes.

Any objections from the Defense?

MR. BECK: No.

THE COURT: Okay.

MR. SAYLES: May it please the Court.

THE COURT: Yes.

MR. SAYLES: At this time, we will read two stipulations and a few requests for admissions --

THE COURT: All right.

MR. SAYLES: -- before our next witness.

THE COURT: Recall that the stipulations are deemed to be conclusive -- conclusively established and in the event a fact is admitted, that that is conclusively established.

MR. SAYLES: Stipulation No. 10: A person of ordinary skill in the art of the '775 patent is a person having a Ph.D. degree or equivalent experience in molecular biology or a related discipline and having a few years' experience in the field of antibody technology.

Stipulation No. 8: The antibody in Humira is known as D2E7 or adalimumab.

All right. Request for Admission No. 19: Admit that adalimumab is an isolated antibody.

Response: Admitted.

Request for Admission No. 2: Admit that adalimumab is a recombinant antibody.

Response: Admitted.

Request for Admission No. 1: Admit that

adalimumab is an anti-TNF-alpha antibody.

Response: Admitted.

Request for Admission No. 3: Admit that adalimumab has a human constant region.

Response: Admitted.

Request for Admission No. 5: Admit that adalimumab binds to a neutralizing epitope of human TNF-alpha in vivo.

Response: Admitted.

Request for Admission No. 7: Admit that adalimumab has an affinity for human TNF-alpha of at least 1 times 10 to the 8th power liters per mole measured as an association constant, as determined by Scatchard analysis.

Response: Admitted.

Request for Admission No. 8: Admit that adalimumab has a human variable region.

Response: Admitted.

Request for Admission No. 32: Admit that adalimumab has a light -- a light chain encoded by a gene derived from human DNA.

Response: Admitted.

Request No. 33: Admit that adalimumab has a heavy chain encoded by a gene derived from human DNA.

Response: Admitted.

Request for Admission No. 12: Admit that adalimumab is of the IgG1 immunoglobulin class.

Response: Admitted.

THE COURT: Who will be your next witness?

MS. MULLIN: May it please the Court. Plaintiffs call Dr. Adams.

THE COURT: Okay.

COURTROOM DEPUTY: Would you raise your right hand, please.

(Witness sworn.)

GREGORY ADAMS, PLAINTIFFS' WITNESS, SWORN

DIRECT EXAMINATION

BY MS. MULLIN:

Q. Would you please state your name for the record.

A. Sure. My name is Gregory Adams.

Q. And could you briefly describe your educational background starting with college?

A. Definitely. I received my bachelor's degree from the University of California at Santa Cruz, and then a Ph.D. in immunology from the University of California at Davis in 1991.

Q. And did you have any particular focus on your

subject matter when you were getting your Ph.D.?

A. Yes. My Ph.D. work focused on using antibodies to target cancer and treat cancer, characterizing the antibodies, looking at the way the antibodies were eliminated from the body during treatment, and targeting --

COURTROOM DEPUTY: Move your microphone.

THE WITNESS: Is that better?

Q. (By Ms. Mullin) Would your kids be surprised to hear that you can't be heard?

A. Actually, sometimes I am a little louder with my children. That's true.

Q. Have you had a chance to continue any of the work that you did for your Ph.D. since you got that degree in 1991?

A. Yes. After 1991 -- essentially, all of my work since 1985 has focused on working with antibodies. And since I got my degree in 1991, I continued to work on developing antibodies and characterizing them for the treatment of cancer.

Q. Where do you do that work?

A. I'm a scientist at Fox Chase Cancer Center. And my position -- I'm a principal investigator, the head of a research laboratory at Fox Chase Cancer Center. I'm a tenured member of the Department of

Medical Oncology. I'm also the co-leader of the Molecular and Translational Medicine Program, and I'm an associate professor at the Temple University School of Medicine as well.

Q. I'm sorry. How long have you been with Fox Chase Cancer Center?

A. In 1991, September '91, right out of graduate school, I went to Fox Chase Cancer Center to something called postdoctoral -- postdoctoral studies. It's additional training after you get your graduate degree, your doctorate, to further expand your scientific skills.

THE COURT: Doctor, this lady here has to take down everything you're saying, okay? So if you could slow down talking just a little bit, it would help her and help the jury, too, I'm sure, okay?

THE WITNESS: Thank you.

THE COURT: Thank you.

Q. (By Ms. Mullin) Can you describe some of the responsibilities that you have as part of your job at Fox Case -- Fox Chase Cancer Center?

A. Yes. As a laboratory principal investigator, I supervise postdoctoral associates. Like I was a trainee in that role when I first came to Fox Chase. I supervise graduate students, students who are studying

to get their own Ph.D.s or master's degrees. I head a research team. I develop the protocols for the experiments with the team. I review the data that comes from the studies, once again, with antibodies.

I help them develop strategies for engineering new antibodies for expressing the protein -- protein targets of the antibodies that we are making in my laboratory.

I also am on a lot of committees. I chair the Radiation Safety Committee at Fox Chase Cancer Center. And as I said, I'm in leadership of the Molecular and Translational Medicine Program, which involves establishing interactions between other members of the faculty and heading -- developing new products.

Q. Is any part of your job involving writing articles for scientific journals?

A. Yes. I write articles. I write grants to fund my lab. I have written over 75 articles that have been published.

Q. And very generally, what's the subject matter of the articles that have been published?

A. Essentially, all of them are on antibodies.

Q. If you could turn, please, Dr. Adams, to what has been marked as Plaintiffs' Exhibit 366.

MS. MULLIN: And, Mr. Ficocello, if you

could please pull that up on the screen.

Q. (By Ms. Mullin) What is this, Dr. Adams?

A. This is my resume.

Q. It goes on for quite a few pages. What's included in this resume?

A. This is my complete resume, so this resume actually includes my education and training, my professional positions that I've had throughout my career.

It includes a list of my talks, the major talks that I've given at conferences that I've been invited to speak at. It discusses my grant-funding history, the trainees that I've trained in the laboratory, the publications that we've presented, and the service I've done in terms of committee work or acting as a reviewer of grants from other scientists for the National Institute of Health, the Department of Defense, the American Cancer Society, and a number of other organizations.

MS. MULLIN: Your Honor, at this time, we proffer Dr. Adams as an expert in antibodies and immunology.

THE COURT: I will allow him to offer opinions in keeping with his expert report.

Did you have anything else, Mr. Lee?

MR. LEE: Nothing, Your Honor.

Q. (By Ms. Mullin) Okay. Dr. Adams, we've heard already some discussion about antibodies, but since this is going to be important to our discussion today, very briefly can you describe the structure of an antibody for the jury?

A. I would be happy to. I believe we have some slides prepared for this.

Q. I think you may actually be controlling the slides yourself.

A. Okay. There we go.

So you've seen this structure before. This is a general illustration of an antibody structure. And as has been said before, antibodies are a Y-shaped structure in general, composed of four chains. The two heavy chains are shown here in blue, and they are identical to each other. And then there are two light chains shown in green that are also identical to each other.

Q. And is there another way that we refer to the different parts of an antibody?

A. Yes, definitely.

And they're particularly relevant to what we're talking about today. Antibodies can be divided -- their structures can be divided into variable domains

and constant domains.

The variable domains shown here in blue are the parts of the antibody that are responsible for interacting with the target protein or antigen that we call.

The parts that are shown in green here are called constant regions, and they are responsible for interactions with the rest of the immune system in terms of eliminating pathogens and stuff like that.

Q. Is this what an antibody really looks like?

A. No. This is how -- that little Y-shaped structure is how we as scientists often depict antibodies in our own textbooks and in talks that we're giving to each other for simplicity's sake.

The structure on the right is -- it's also similarly coded in colors, is a much -- sorry -- a much more accurate structure of an antibody. It's a molecular model of an antibody.

Q. Can you describe how an antibody interacts with an antigen?

A. Definitely. So --

Q. Maybe before you do that, what's an antigen? That might be a relatively new word.

A. So an antigen is the target of the antibody. It typically -- we've heard it described already today

as a pathogen, such as a bacteria. It could be a flu virus; it could be the surface of a tumor cell, some marker on the surface of a cancer cell in the patient's body.

But the antibody recognizes that antigen. We use the term antigen. It's highly specific for the antigen and recognizes it in its own manner.

And the way it recognizes the antigen is using the very tips of the Y structure.

Let me see if I can get this working.

The tips of the Y-structure here that were the equivalent of the very tops of the arms of the Y, and it binds to the surface of the antigen here.

Q. Okay. Is there a particular name for that very typical Y-structure?

A. Yes. We call that the complementarity determining regions, or the CDRs of the antibody that are shown here in yellow on the tips of the blue part of the antibody. They're also part of the variable region.

Q. Now, we've also heard a very little bit about affinity.

Generally, what does affinity refer to?

A. So, generally, affinity refers to the strength of the bond between the antibody and the antigen, how tight that bond is, how is -- how well they hold

together.

Q. And do different antibodies have different affinities?

A. Definitely. Antibodies -- affinities of the antibodies are dictated by the amino acids that make up the complementarity determining regions shown in yellow here.

So if you have amino acids that pair well with the amino acids on the antigen, you'll get a nice, strong affinity. If they don't pair quite as well, the affinity will be weaker, and the bond will often be more transient and come apart faster.

Q. How does the human body make antibodies, just very briefly?

A. Very briefly, the cells in the human body known as B-cells or B lipocytes, and when antigens present to those cells, they make antibodies. And there's -- what's remarkable about the system is that the B-cells in our bodies can make millions of different antibodies. It's really a remarkable system.

Q. Now, we've heard the word recombinant used already today.

Are recombinant antibodies generally made in the same way as you just described for antibodies made in the human body?

A. Yes and no.

The general -- recombinant antibodies, like natural antibodies, are made using DNA instructions that come from inside the cell.

Recombinant antibodies are made in a way that we've modified the DNA to give it new instructions to make a somewhat different antibody. But it's still using the same type of machinery in the cell to make the antibodies.

So it's still the cell producing it.

Q. And does recombinant refer to generally something done or that can be done in a laboratory?

A. Yes, it can. In fact, it's the basis of the antibodies that we're talking about in this case, that they have been -- they're using tools -- using tools in the laboratory to connect the DNA in different ways to make the antibody.

I think there are some slides here that might help with that.

Q. Maybe you can use the slides to explain very generally how it is that antibodies are engineered or with the process of engineering.

A. Sure, in general terms.

A little bit earlier today, it was mentioned that there are 20 amino acid building blocks to make

antibodies, and these have letter codes. These are not arbitrary codes. They actually stand for the names of the amino acids.

So, for instance, the A here is alanine. There's valine, et cetera. These are standard, accepted names for the antibodies.

And when you make an antibody or any other protein, whether it's fingernail or it's an ear of corn, it's the order of these amino acids that dictate what that protein is going to be.

And to make that, what happens is our body, the cell, uses DNA, which is shown or illustrated here as a double helix twisting ladder. And that is really the instruction booklet for the cell, telling the cell what order to put these amino acids into to make this protein.

And if you have a different instruction booklet or a different sequence of DNA, you'll get a different sequence of amino acids, which will make a different protein.

But these amino acids are all the same amino acids, as I said, whether it's making a tree or a person.

Q. So what does the word recombinant or the genetic-engineering part? Where does that come in?

A. So recombinant, as I said, is putting together two different pieces of DNA. So if we have the white double helix, the twisted ladder here, it would be the Instruction Sheet No. 1. It's what that piece of DNA is equivalent to, while the yellow DNA would be a separate instruction sheet.

If you cut the white piece of DNA and insert a piece of the yellow DNA here, what you'll get is part of the protein or antibody that was encoded for by the white piece with a different piece inserted inside. And this is genetic engineering, or recombinant DNA technology are the common names for this.

Q. I would like, then, to move into the more specifics of this case. And I think maybe you could bring up the next slide.

Yeah. Do you recognize this?

A. Yes. This is the '775 patent.

Q. This is -- I'm sorry.

A. I'm sorry. Go ahead.

Q. Now, it's also been marked as Plaintiffs' Exhibit 1. I would like to point out.

Were you asked to review the '775 patent for purposes of this case?

A. Yes. As an expert witness in this case, that was one of my tasks.

Q. And were you also asked to consider Abbott's Humira product for purposes of this case?

A. Yes, I was.

Q. Now, we've been referring to Humira, but is there a specific name for the antibody in Humira?

A. Yes. The name is adalimumab. And the antibody in Humira, well, I will refer to it as Humira most of today just because it's much easier for all of us if we call it Humira.

Q. Now, I think you were here when Judge Ward gave some instructions this morning. But you recognize that in terms of assessing infringement, what you're really looking for is the -- is the -- its me speaking up now. I'm sorry.

What you're really looking for is to compare the Humira antibody, or adalimumab, to the patent claims, right?

A. That is my understanding, yes.

Q. Okay. Now, does the '775 patent claim all antibodies against TNF?

A. No, it does not. It claims antibodies that bind to TNF in a certain manner with a certain strength or affinity and with a certain composition.

Q. Then I think we have a slide that has put Claim 2 on it.

A. Let's see if I can get that going.

For some reason -- that might do it.

Q. There we go.

Claim 2 would be the first asserted claim in the patent that we're going to be discussing today. And if you could just walk us through.

What are the different elements of Claim 2?

A. I would be happy to.

Claim 2 is a dependent claim, which means that it must include all -- it's dependent upon Claim 1. It must include the elements of Claim 1 as well as a particular element of Claim 2.

And I'll explain that right here.

So the elements in Claim 1, what is claimed is an isolated recombinant anti-TNF-alpha antibody. It must have a human constant region. It must competitively inhibit the binding of A2, which is ATCC Accession No. PTA7045, to human TNF-alpha.

It must bind to a neutralizing epitope of human TNF-alpha in vivo.

And it must have an affinity of at least 1 times 10 to the 8th liter per mole measured as an association constant, or Ka, as determined by Scatchard analysis.

And then the piece of Claim 2 or the element

in Claim 2 that's added on is it must have a human variable region.

Q. Dr. Adams, do you have an opinion as to whether the Humira antibody includes each element of Claim 2?

A. Yes, I do.

Q. And what is that opinion?

A. My opinion is that it does and it infringes.

Q. Let's walk through that, then, if we can element by element.

A. Sure.

Q. I think if --

A. So we'll start with the first element, isolated recombinant anti-TNF-alpha antibody. And I've looked at the literature, the documents from Abbott, and looked at it specifically to determine whether or not it's an isolated recombinant anti-TNF-alpha antibody. I concluded that it was.

And as you recall from what was read into the transcripts just before I came up, Abbott has also admitted that fact. So, in fact, we can check off that box here, that it is an isolated recombinant anti-TNF-alpha antibody.

Q. Okay. What's the next element in the claim, Dr. Adams?

A. The next element in the claim is that it must have a human constant region. And, again, I have reviewed the literature, and I've come to the conclusion that Humira has a human constant region.

And, in fact, again, Abbott was asked to and has admitted that it has a human constant region. So we can check off that box.

Q. And, again, the constant region is part of the antibody structure?

A. Yes. If you'll recall when I was talking about the Y-struct of the antibody, the constant region was the bottom part of the antibody, not the part that binds to the antigen.

Q. And what is the third element of Claim 2?

A. Okay. The third element is competitively inhibits binding of A2, ATCC Accession No. PTA7045, to human TNF-alpha.

Q. Okay. Stop for a second, please.

There's a reference to ATCC Accession No. PTA7045.

What is that?

A. So let's start with ATCC. ATCC stands for the American Type Culture Collection. It's essentially a library of sorts where scientists deposit cell lines that are of interest to other scientists. Other

scientists can then request the cell lines for their own experiments.

And then the accession number, PTA7045, is just that; it's the name that ATCC has given the cell line that expresses A2 antibody.

Q. And do you have an understanding as to whether the Court has provided us with some guidance as to what the phrase, competitively inhibits binding of A2 to human TNF-alpha means?

A. My understanding is that it means competes with A2 for human TNF-alpha.

Q. Okay. So let's start first -- you said competes with, but can you first very briefly describe what are noncompeting antibodies?

A. Well, if you -- if you have an antigen, noncompeting antibodies would be antibodies that can bind at the same time.

Q. But now let's talk about the reverse.

How do you know or how do you test whether antibodies are competing antibodies, whether they compete with each other?

A. Well, what I'll do is I'll explain to you an example of how scientists would test for this. I think it's shown on the next slide.

Susan Tam, a few minutes ago, talked to you

about 96 well plates, the plastic plates. And what the scientists will do is bind TNF in this case, which is the target we're interested in, to the bottom of the plastic plate.

Q. I'm sorry. Because of the way it's shown there, is TNF really like a slab of cake icing?

A. No. This is -- once again, this is an illustration for convenience. TNF is -- it's a globular -- it's like a ball-shaped protein. It's protein per trimer. It's really three proteins brought together.

But we can bind it to the bottom of the plate and use that as a tool for measuring how the antibodies compete with each other.

Q. So if you could proceed with an example of the way you test for competition, that would be great.

A. Sure.

Q. Thank you.

A. So what we do is if this was anti-TNF-alpha antibody, we would label it -- and, once again, we have a Y-shape. And we're labeling the antibody with a tag or a tracer such as a radioisotope, which is shown by this starburst color here.

Q. I'm sorry. Radioisotope is what?

A. A radioisotope is a radioactive particle that

allows us to follow the antibodies that have the radioactive particle on it.

So in this case, it could be Iodine-125, which is a commonly employed radioactive particle.

And we put these in solution, in fluid, and apply them to each well of a 96-well plate and allow them to bind to the surface of the TNF-alpha on the plate.

Q. Okay. I'm sorry. You said a 96-well plate. Is this one well or 96 wells being shown here?

A. This is one well that's being shown. You could do it as individual wells, but it would just take a long time and be a lot of work. It's much easier and much more consistent to be able to use a 96-well plate and do the assay all at once.

So we allow the antibodies to bind to the surface of the plates typically over the course of something like two hours. And then we wash off the amount of -- the antibodies that have not bound and measure the bound antibody.

Ms. Tam talked about measuring it in an instrument called a gamma counter. And if it's Iodine-125, that's an appropriate tool to use. And then we can -- with that measurement, we can graphically indicate the amount of antibody that's bound

to each well of the plate in a graph.

So in this case, when we have just the one antibody with the radio label bound to TNF, we get a certain amount of radioactive counts on the graph.

If we add -- let's see if I can get this going.

If we add some antibodies without a label that we think that the antibodies may compete with each other, the labeled antibody and the unlabeled antibody, and we add them together and allow them to bind to the TNF-alpha on the bottom of the plate, what you'll notice is that there is less label being bound to the surface of the plate.

And we wash off the unbound antibodies, and we see a decrease in the amount of label that's measured in the machine that we show on the graph.

If we increase the amount of unlabeled antibody, what we get -- and, once again, incubated over time, wash off the unbound, what we get is even less of the radioactive tracer. We call it a tracer, the radioactive molecule being measured on the plate.

Now, we continue to do this through a number of series of dilutions, and this leads to a situation here where you can see that we're seeing a significant decrease in the amount of radiolabel on the graph that

represents the amount of radio-labeled antibody being bound to the plate.

This indicates to us that the antibodies are competing with each other.

Q. Is there a kind of characteristic curve or something that you get in the graphs when there's competition?

A. Definitely. Typically, you see something that we often call an S-shape curve where you see a plateau, a drop, and then another plateau. And this is typically the sign of an assay that's working well.

Q. Now, were you in the courtroom when Ms. Tam was testifying today?

A. Yes, I was.

Q. And before she testified today, had you had an opportunity to talk with her about her work?

A. Yes, I had.

In fact, I'd like to show you one more slide, if you don't mind.

Q. I'm sorry.

A. I had one more, I believe.

And this one is what happens when you have an antibody that does not compete. And that we have two antibodies that don't compete with each other. And we're just showing this with this U-shape instead of the

Y-shape, a U with a tail.

And in this situation, what happens is even if we have a lot of the antibody that does not compete present, we should get the labeled antibody binding without -- without a decrease to competition.

And this will happen even if we increase and decrease the amount of noncompeting antibody. You'll get a fairly straight line that represents noncompetition.

Thank you.

Q. Is there another slide, Dr. Adams?

A. Hopefully, that's it.

Q. Were you in the courtroom, then, when Ms. Tam was describing her testing?

A. Yes, I was.

Q. Okay. And before today, did you have a chance to talk with her about what she had done and talked through her results with her?

A. Yes, I did. I spent at least half a day with Ms. Tam going through her results, going through her notebook in detail, looking at the way she set up the assay. I had her walk me through it.

We went through the calculations she did, and I looked at how she did them and had her do them for me again. And I did some of them as well. I looked at the

results, the data that came from this assay. I looked at the graphs. I discussed all aspects of the work with her.

Q. Did you do anything to verify that she was using the right antibodies in her testing?

A. I -- I did some -- it's really not detective work, but I -- one of the assays she did was an affinity measurement in something called a Scatchard analysis. You've heard that the term before.

So I looked at the affinity that she measured of Humira, the radio-labeled Humira. And I compared it with what Abbott reports as the affinity for Humira, and I found them to be comparable, which led me to conclude that she did, in fact, use Humira in that assay.

And then for the A2 antibodies that she was using in the competition assays, I actually sequenced those antibodies. And I looked at the sequences and compared them with the known sequences for A2 and was able to conclude that she did use A2 as well.

Q. Now, Dr. Adams, I believe you have a copy of Plaintiffs' Exhibit 854, which is Ms. Tam's notebook in front of you.

If you could please open that.

A. Yes, I do.

Q. And generally, what is shown on Pages 18

through 21 and 24 through 25 of her notebook?

A. So on these pages, she describes the assay set-up, the materials she used, the conditions she did the assays under. She also describes and provides the data from these assays, the results, the calculations that she performed on the assays, and then the graphical representation of the results of the assays.

Q. Okay. If we can stop at Page 21 for a minute. Can you describe what's shown on Page 21 of Ms. Tam's notebook, PX854?

A. Sure. This is the data that comes out of the machine, the gamma counter that counts the radioactive antibodies in the microtiter plate, the 96-well plate. And what this does is it gives us or gave her really the counts per minute, cpm, the actual radioactivity that was an indication of how much antibody was bound in each well.

And if you scroll down, you'll notice that there are counts in 96 rows. Each row is one well going across here. So if we go all the way down, we'll see that after 96 wells, the counts go away.

You will also notice that there are two sets of columns, and that's because she did the assay in duplicate as she said during her testimony. And so this assay was done with two sets of identical wells to

measure the competition.

Q. Is this what she meant when she said she did the assay twice?

A. No. This is the duplicate for one assay. She did it again in duplicate a second time. So each time she did the assay, she did the assay twice. Each time she did it, she had two identical sets of wells.

MS. MULLIN: If Mr. Ficocello then could please bring up a split screen, which would show us Pages 23 and 26 of Ms. Tam's notebook side-by-side.

Q. (By Ms. Mullin) What is shown here, Dr. Adams?

A. So this is the graphical representation of the results, and let me just talk you through it, because it is a bit complicated.

What we have here in identical -- it's really, once again, the layout is identical. But we have on the left going up and down, this line up and down shows us the amount of counts per minute, or cpm, that are bound to the plate.

And so the higher it is, the more radioactivity, and, therefore, the more Humira is bound to the plate.

And then on the bottom line that goes left to right, what we have here is the amount of antibody that's been added that is not labeled with

radioactivity. This is the antibody that we're measuring to see if Humira and that antibody compete with each other in an assay like this.

So what you see, if you're going off to the left to the right, is increasing concentrations, increasing amounts of the antibodies that we are testing against Humira.

And what we see here is that as you go out to the right, the amount of bound counts, or the amount of radio-labeled Humira that are binding to the TNF-alpha on the plate decrease.

She did this twice, and we see it in both situations.

Q. Now, what we see here on this split screen, this is not the duplicate data. These are the two different experiments, right?

A. That is correct. On the left is Experiment 1, I believe; and on the right is Experiment 2.

And what you see actually here -- it's even clearer on this one -- is the negative controls that are not going down because there is no competition.

The negative controls do not -- and Humira do not compete with each other, so there is no drop in the counts for Humira.

Q. So what conclusions, if any, could you draw

from the first duplicate competition assay experiments Ms. Tam did with Humira and A2?

A. So from the first duplicate, I concluded that had Humira and A2 compete with each other.

Q. And what conclusion, if any, did you have from her second competition assays done in duplicate?

A. And it's just as clear. From her second competition assay, it's very clear to me that Humira and A2 compete with each other for human TNF-alpha.

Q. Now, when you were describing generally how competition assays were done, you talked about labeling an antibody; is that correct?

A. That's correct.

Q. Okay. Which antibody was labeled for purposes of Ms. Tam's experiments?

A. Humira.

Q. Does it matter whether it was Humira-labeled or A2-labeled when you're testing for competition in this kind of assay with these kinds of antibodies?

A. No, not at all. I've been working in this field, as I said, since 1995. I've worked with many antibodies. I've been radio-labeling antibodies since 1995.

And in my experience, it does not matter. I have not, in my laboratory, that I recall, ever have

seen that it matters with two full-size antibodies in measuring competition with each other for an antigen.

Q. Could there be some very rare occurrence that would cause a quirky result?

A. Yes. There are tens of thousands of articles about antibodies and antibodies that bind to targets. And I've seen over the years a handful, just literally a handful of publications that when an antibody has some strange properties -- for instance, it doesn't function as well at low temperature or functions better at low temperature or the antigen has quirky properties that are not typical of other antigens, particularly very large antigens or antigens on the surface of cells, you might sometimes see a difference, but it's very rare.

Q. Now, you know that Abbott has criticized what Ms. Tam did and said she should have labeled the A2 instead of the Humira, right?

A. Yes, I do know that.

Q. So, again, in your experience, in your opinion, does it make a difference which antibody was labeled here?

A. Not at all.

Q. Do you have any -- anything that can back up your opinion on that, any support for your opinion that it doesn't matter here?

A. Well, there's -- besides my experience, there's a number of assays have been done at both Abbott and Centocor with looking for the competition between Humira and chimeric A2, the cA2 antibody that we've talked about here today.

And in all of those experiments, they all clearly show that these two antibodies compete with each other. There is no evidence that I've ever been shown that they do not compete with each other.

Q. Dr. Adams, you're now talking about assays involving chimeric A2 or cA2 for the antibody in Remicade rather than assays involving A2, Humira. So how can you equate or relate assays using cA2 to assays that use A2?

A. So if you recall, when we talked about the Y-shaped antibody structure, that the constant domains are on the bottom and the variable domains are on the top.

The variable domains are the tips of those arms -- or the top of the arms of the antibodies are the parts that actually dictate the specificity of the antibody for the antigen. They're the part that interacts with the antigen or TNF-alpha in this case. Since chimeric A2 and A2 have identical variable domains, and one of the inventors from Centocor earlier

today said those domains were identical, they will bind to the same spot in the same manner.

So if chimeric A2 and Humira compete with each other, A2 and Humira will also compete with each other.

Q. Dr. Adams, I believe in your binder of exhibits, you have what's been marked as Plaintiffs' Exhibit 137. If you could find that in your binder, please.

MS. MULLIN: And perhaps Mr. Ficocello could bring that first page up on the screen that's been preadmitted.

Thank you.

A. Yes.

Q. (By Ms. Mullin) What -- what is this document?

A. So this is one of the tests that I told you about that have been happening at both Abbott and Centocor. And the tests that I'm referring to were performed before the lawsuit, before the litigation. And to be honest, I was not privy to them. I don't know why they were performed. I just have seen the results of these tests.

The document here is showing a test that was done at Abbott by Zehra Kaymakcalan. I'm sure I mispronounced her last name; I always do.

And this test was competition assays where she

was showing competition between chimeric A2, or Remicade is the other name, and for the Humira.

Q. Okay. Was this lawsuit filed before July 1st, 2005?

A. No.

Q. If you can turn, then -- and perhaps Mr. Ficocello could help us again bringing up the pages that end in 451 and 452 as a split screen.

Can you describe what's been depicted here in this Abbott document?

A. Sure.

Now, these are, once again, competition assays. And what we're seeing here is that on the left, the Humira antibody has been labeled with Iodine-125, and on the right, Remicade, the chimeric A2, was labeled with Iodine-125.

And these are very similar to what I described a few minutes ago and described the competition assays, except that in this case, instead of going down, now we have percent inhibition on the up-and-down side on the left here.

Q. Okay. I'm sorry. So can you explain that a little more, because before we were talking about something that looked kind of like a 2, and now we're looking at something that looks kind of like an S.

A. Exactly.

So what's happening here is, since we're measuring competition, it's sort of the inverse. The more competition, the less counts it would be.

So if we measure the amount of counts instead of the competition, it would be a curve going this way. But since we're measuring how much of the labeled antibody is prevented from being bound when they're competing with each other with the unlabeled antibody, if the unlabeled antibody is causing competition with the labeled antibody and vice versa, which you will get an increase in inhibition with the antibodies.

And if you look closely here, you'll see that Remicade causes inhibition with Humira. Humira causes inhibition with Humira, et cetera.

And on this side, Remicade causes inhibition with Remicade, and Humira causes inhibition with Remicade.

Q. Again, there are some other substances that were being tested here, right?

A. Yes. There are controls and there is something else called an Enbrel, which is another molecule that targets -- it's not antibodies, but something else that targets TNF-alpha.

Q. Okay. But in each one of these tests, Humira

and the chimeric A2, the Remicade antibody, were used?

A. Yes. And in each one of these tests, they compete with each other.

Q. Okay. And is there any difference between these other than whether it's the Humira or the cA2 that's labeled?

A. I'm sorry. Any difference between the two tests or --

Q. Yes.

A. Between the test on the left and the test on the right, they are really identical assays, except that we're labeling Humira or cA2.

Q. And what do those assays demonstrate?

A. Well, what they demonstrate to me is that Humira and chimeric A2 compete with each other and, therefore, demonstrate to me that A2 and Humira would compete with each other as well.

MS. MULLIN: If you can go back, then, to the slides that Dr. Adams controls.

Q. (By Ms. Mullin) And so we started this, and I think if we go maybe one or two more slides, we'll come back to where we started.

We started this conversation talking about the element competitively inhibits binding of A2, ATCC Accession No. PTA7045, to human TNF-alpha.

Dr. Adams, do you have an opinion as to whether Humira meets this element of Claim 2?

A. So based on what I just showed you, I conclude that Humira does meet this -- this claim.

So we can check that off.

Q. What is the next element, then, in Claim 2?

A. So the next element in Claim 2 is that it must bind to a neutralizing epitope of human TNF-alpha in vivo. And I looked at the data and the results or at the publications. I concluded that it does.

And, in fact, once again, Abbott has admitted that it does as well. So we can check that box off.

Q. I'm sorry. And when it's talking about binding in vivo, what's that referring to?

A. So binding in vivo is referring to the function. In vivo means antibody in a mouse, in a human. It means that it is functional in a living creature, really.

Q. And what's being specified here, though, is binding to human TNF-alpha in vivo, right?

A. That's correct. So it means that we're not talking about binding to mouse TNF-alpha or rhino TNF-alpha; we're talking about human TNF-alpha, which is a critical component of this claim.

Q. And did Mr. Sayles read something in before

you started relevance to --

A. Yes. I'm sorry. He did also read in that Abbott has admitted that Humira binds to human TNF-alpha in vivo.

Q. So what does -- I'm sorry.

A. Let me check that off.

Q. Okay. So what is the next element of Claim 2?

A. So the next element is that it has an affinity of at least 1 times 10 to the 8th liter per mole, measured as an association constant, or Ka, as determined by Scatchard analysis.

And once again, I've looked at the literature on Humira. I have looked at Susan Tam's testing data, and I've concluded that it meets this claim that it has at least an affinity of 1 times 10 to the 8th liter per mole.

And, in fact, Abbott has also been asked to and has admitted that fact. So we can check that off as well.

Q. Really briefly, what does association constant or Ka refer to?

A. So when we were talking about affinity before, association constant is a measurement of the affinity, measurement of the strength of binding.

And in this case, as that number goes up, the

antibody and the antigen have a stronger bond for each other than if the affinity number was lower.

Q. And the reference there is Scatchard analysis. If you can explain that just very briefly.

A. Very briefly, a Scatchard analysis is a type of analytical study that's done on these binding studies. It's a way of looking at the data to conclude what the affinity is, the strength of binding of the antibody for the antigen.

Q. Then what is the element that is added by Claim 2?

A. The element added by Claim 2 is a human variable region. And, once again, I've looked at the documents, and I've concluded that Humira has a human variable region.

Abbott was asked to and has admitted that it has a human variable region, so we can check that off as well.

Q. So, Dr. Adams, what is your opinion as the to whether the Humira antibody infringes Claim 2 of the '775 patent?

A. It's my opinion that it does infringe.

Q. Can we move to Claim 3 then? That's the next asserted claim in this patent.

A. Definitely.

Q. Can you describe -- what are the parts of Claim 3?

We've got a lot of underlining already up there.

A. Well, the reason we have a lot of underlining up there already is Claim 3 is also a dependent claim. Just like Claim 2, Claim 3 also depends on Claim 1.

And since we already went through Claim 1 in detail, what we've seen is we've checked off -- gone through and underlined a lot of these points that we've already checked off for Claim 1 when it was a dependent claim, when it was being used by Claim 2.

And now what we're focusing on is this additional two components in Claim 3, or these additional two elements, the human light chain and the human heavy chain.

Q. And does Humira have a human light chain and a human heavy chain?

A. Yes, it does. Once again, I've looked at the documents, and Abbott has also admitted it.

So we can check off that it has a human light chain and a human heavy chain.

Q. So do you have an opinion as to whether the Humira antibody infringes Claim 3 of the '775 patent, Dr. Adams?

A. Yes. It is my opinion that it does infringe Claim 3.

Q. The next asserted claim in this case is Claim 14. Now, you have a lot of things up there.

What's -- what are the elements of Claim 14?

A. So, once again, the elements of Claim 14 are the same as the elements of Claim 2. So when we've already gone through and checked off the elements of Claim 2, and it's sort of a stacking game. We keep adding more things in, but we've checked off those elements.

But with Claim 14 adds -- I'm underlining here in blue -- is a human IgG1 constant region.

Q. I'm sorry. What is IgG1?

A. So IgG1 is a class of antibodies. There are five classes of antibodies that are in human bodies. There is IgG, IgA, IgD, IgM, and IgE. And IgG1 is one of these classes.

And I've looked at the documents and have concluded that Humira is a human IgG1 or has an IgG1 constant region. And Abbott has also been asked to admit that and has admitted that it has a human IgG1 constant region.

Q. Now, Dr. Adams, do you have an opinion as to whether Humira or the Humira antibody infringes Claim 14

of the '775 patent?

A. Yes. It is my opinion that it infringes Claim 14.

Q. And just to be clear, other than the human IgG1 constant region that's referenced here, the analysis that we walked through before for all the other elements, is it all the same for these elements of the claim?

A. That is correct. This is the only new element that is added on to all the other elements that I walked you through already.

Q. Okay. Claim 15, I believe, is the next asserted claim. And, again, we have it lined up next to Claim 3. Why is that?

A. Because once again, Claim 15 -- we've already gone through all those elements in Claim 3, a dependent claim. And we have concluded, once again, that all these elements were satisfied by Claim 3 when we walked through that.

And what's added here again is a human IgG1 constant region for the reasons that I just stated and for Abbott's admission that it is an IgG1 constant region. And we can go ahead and check that one off as well.

Q. So, Dr. Adams, do you have an opinion as to

whether the Humira antibody infringes Claim 15 of the '775 patent?

A. Yes. It is my opinion that it infringes Claim 15 as well.

Q. So maybe we can -- I think there's a summary slide.

A. Yes.

So this slide shows all the checked boxes that I've just gone through showing you that Humira infringes these claims. And, in fact, everything in red are the checked boxes that Abbott has already admitted that Humira infringes on the '775 patent.

And then in blue is the part about competitively inhibits, which I walked you through in the studies that were done at Abbott and Centocor.

Q. To make sure I didn't miss any, then, what is your opinion as to whether Humira infringes Claims 2, 3, 14, and 15 of the '775 patent?

A. It is my opinion that Humira infringes Claims 2, 3, 14, and 15 of the '775 patent.

Q. Dr. Adams, other than the conversations and time spent working on this case, do you have any financial interest in any of the parties in this litigation?

A. No, I do not.

Q. Does the compensation that you receive for your time depend in any way on the content of your testimony?

A. No, it does not.

Q. Does it depend on your conclusions?

A. No, it does not.

Q. Does it depend on the outcome of your analysis?

A. No, it does not.

Q. Thank you.

MS. MULLIN: I pass the witness.

MR. LEE: May I have a minute, Your Honor?

THE COURT: Certainly.

(Pause in proceedings.)

THE COURT: Proceed, Mr. Lee.

MR. LEE: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. LEE:

Q. Good afternoon, Dr. Adams.

A. Good afternoon.

Q. Dr. Adams, you work at the Fox Chase Cancer Research Center, correct?

A. The Fox Chase Cancer Center is the name, that's correct.

Q. And the center specializes in cancer research, correct?

A. That is the major focus of the cancer center. If you'd like, I can tell you about the additional focus.

Q. No. That's okay. But that's the major focus of the --

A. It's the major focus, though we have a very strong immunology group as well in the Basic Science Division.

Q. Now, this case is about anti-TNF-alpha antibodies, correct?

A. That's correct.

Q. You have never made a mouse anti-TNF-alpha antibody, have you, sir?

A. That's correct.

Q. You have never made a chimeric anti-TNF-alpha antibody, have you, sir?

A. That is correct.

Q. You have never made a fully human anti-TNF-alpha antibody, correct?

A. That is correct.

Q. In fact, Dr. Adams, before you got hired to work in this case, you have never worked at all with anti-TNF-alpha antibodies, correct?

A. That is correct.

Q. The first time that you were asked to work with anti-TNF-alpha antibodies is when a lawyer called you to work in this case, correct?

A. Well, actually, I've never worked with anti-TNF-alpha antibodies.

Q. Fair enough.

Now, when is the first time you heard of the '775 patent?

A. When I was asked to serve as an expert witness on this case.

Q. And when was that?

A. It would have been September of last year.

Q. Okay. So September of 2008, correct?

A. That's correct.

Q. So before September 2008 -- September of 2008, even though you've worked in the field since 1990 -- 1985, correct?

A. That is correct.

Q. So 23 years, correct?

A. That's correct.

Q. You've never heard of the '775 patent, correct?

A. Not of the patent, that is correct.

Q. And before you were asked in September of 2008

to work with Centocor's lawyers, you had never made any analysis of any kind of an anti-TNF-alpha antibody, murine, chimeric, or human, correct?

A. That is correct.

Q. Now, your testimony today concerned the issue of infringement, correct?

A. Correct.

Q. You haven't provided any testimony on the issue of validity, correct?

A. That's correct.

Q. You mentioned --

A. Not to -- not right now. Not up till now.

Q. Not today.

A. Not today, that is correct.

Q. You may come back to provide that testimony, correct?

A. Correct.

Q. So I'm going to confine my questions just to the question of infringement and leave validity for a later day, okay?

A. That's fine.

Q. Now, I'm going to put on the screen Claims 1 and 2, which you just had on the screen. In the notebook before you is -- are also the hard copies of the exhibits.

A. Correct.

Q. And you use whichever one is most comfortable for you, okay?

A. Okay. That's fine. Thank you.

Q. Now, you've explained that Claim 2 is the claim that's in issue in this case, correct?

A. That is my understanding, yes.

Q. And to figure out what Claim 2 requires, the jury needs to look at both Claim 2 and Claim 1, correct?

A. Because it is a dependent claim, correct.

Q. Claim 2 is dependent on Claim 1.

A. Correct.

Q. And to figure out what Claim 2 requires, you have to figure out what all the requirements are of Claim 1 and Claim 2, correct?

A. Correct.

Q. And to infringe, as you've used that term, the accused product has to have each and every element of the claim, correct?

A. Correct.

Q. If it's missing only one, the jury finds that it's missing only one, then there's no infringement.

A. That is correct.

Q. And that's the judgment -- that's the standard you've brought to bear in your analysis, correct?

A. Correct.

Q. Now, you understand that Centocor has the burden of proving infringement, correct?

A. Correct.

Q. You understand that Humira is the accused product, correct?

A. Correct.

Q. And you understand that that means that Humira needs to satisfy each and every limitation of Claims 1 and 2, correct?

A. That is my understanding, yes.

Q. If there is a single limitation missing, there would be no infringement, correct?

A. Correct.

Q. Now, in Claim 2, there is a requirement of a human variable region, correct?

A. That is correct.

Q. And you understand what that means, correct?

A. Yes, I do.

Q. So Claim 2 does not cover a chimeric antibody, does it?

A. That is correct.

Q. It only covers a human antibody, correct?

A. That is correct.

Q. And the same is true for Claims 13, 14, and

15. They all require a human variable region, correct?
A. Correct.
Q. They don't cover a chimeric antibody, correct?
A. Correct.
Q. And cA2 that you referred the jury to, cA2 is a chimeric antibody, correct?
A. That is correct.
Q. Now, looking at Claims 1 and 2, there is a requirement, competitively inhibits binding of A2, ATCC Accession No. PTA-7045, to human TNF-alpha.
A. Correct.
Q. It's true, is it not, sir, that before you got involved in this case, you had never reviewed any test results to determine competitive inhibition for TNF-Alpha, correct?
A. That is correct.
Q. The first time you ever looked at any test results to try to figure out whether something was competitively inhibiting was when you got hired in this case, correct?
A. Specifically through this case, correct.
Q. Right. And in fact, by the time you were retained in September 2008 -- correct?
A. Correct.
Q. Ms. Tam had run her tests almost a year

before, correct?

A. Correct.

Q. So by definition, you had no involvement in how they determined how she was going to run her tests, correct?

A. Correct.

Q. You had no involvement with the protocol she used, correct?

A. Correct.

Q. You had no input into the manner in which she was going to do them, correct?

A. Correct.

Q. In fact, a year and a half after she did them, the lawyers gave them to you and said, here's what we got, correct?

A. They asked me to analyze it, correct.

Q. Now, for the issue of infringement on which you bear -- on which Centocor bears the burden of proof, you have some testing, and you've testified about it, correct?

A. That is correct.

Q. You understand that on the issue of validity, Abbott has the burden of proof.

A. That is my understanding.

Q. Right. And Abbott, on that -- on those

issues, has done some testing, correct?

A. That is correct.

Q. But you haven't done any testing on validity, correct?

A. I don't --

MS. MULLIN: Objection, Your Honor. What is this?

THE COURT: Well, y'all approach, please.

(Bench conference.)

THE COURT: Well, Mr. Lee, let me tell you where you're headed. You're heading -- I'm going to tell you where you're headed for the record. Where you're headed for the record is, I'm going to let them start talking about, giving opinions about validity, because you're opening the door to it.

MR. LEE: I'll move off of that until he comes back.

THE COURT: Well, that's -- either that or you're not going to like what's going to happen, I tell you.

MR. LEE: Yeah. I'd prefer to like what happens.

MS. MULLIN: I'd like it the other way, Your Honor.

(Bench conference concluded.)

THE COURT: Let's move along now.

Q. (By Mr. Lee) The testing that you did was testing on which you had the burden of proof, correct?

A. The testing I reviewed, you mean?

Q. Yes. I'm sorry. The testing that you reviewed was testing on which you had -- issues on which you had the burden of proof, correct?

A. On which Centocor had the burden of proof, correct. I'm an expert witness. I'm not really a party on either side here.

Q. Right. Now, Dr. Adams, Claims 2, 3, 14, and 15 all require competitive inhibition, correct?

A. That is correct.

Q. So if the testing doesn't prove that Abbott competitively inhibits for Claim 2, there's no infringement of Claim 2, correct?

A. That would be my understanding, yes.

Q. And the same would be true for Claims 3, 14, and 15, correct?

A. That would be my understanding.

Q. And let's start with Claim 1.

Claim 1 begins with the phrase: An isolated anti-TNF-alpha antibody -- I'm sorry.

An isolated recombinant anti-TNF-alpha antibody.

A. That is correct.

Q. That would be Humira in your analysis, correct?

A. That is correct.

Q. And the claim requires that an isolated recombinant anti-TNF-alpha antibody competitively inhibits something, correct?

A. That is correct.

Q. So Humira has to interfere with the binding of A2 and TNF-alpha, correct?

A. They need to interfere with each other.

Q. Well, it says -- the words say: An isolated recombinant anti-TNF-alpha antibody competitively inhibits binding of A2, correct?

A. So speaking as a scientist --

Q. Is that what -- is that what the words say?

A. If you want me to read the words, I'd be happy to read the words to you.

Q. Well, you were here this morning when His Honor said it's the claims that define the metes and bounds for infringement purposes, right?

A. So my understanding is the Court has construed that claim to mean competes with A2 for human TNF-alpha.

Q. Fair enough.

Now, let's use the standard the Court's

articulated, which is in the jurors' notebooks. You've relied on different sets of tests to support your opinion, correct?

A. That is correct.

Q. Now, first, only one set of those tests involve Humira and A2, correct?

A. That is correct.

Q. That's Dr. Tam's test, correct?

A. Correct.

Q. Now, three of the tests you relied upon involved Humira and cA2, correct?

A. That is correct.

Q. Now, you know, sir, do you not, that at one point in time, Centocor had claims pending before the Patent Office that required competitive inhibition with either A2 or cA2, correct?

A. To be honest, I cannot recall that.

Q. Well, let me see if I can show you.

MR. LEE: If I can just have a second here, Your Honor.

Could we bring up DX777, which is in evidence, Your Honor.

Q. (By Mr. Lee) It's at Tab 3 of your notebook.

A. Tab 3? Thank you.

Q. Yeah.

And we'll start with this. Now, I want you to have in mind so that we're all on the same page, we're talking about tests that compare Humira and cA2.

Do you have those in mind?

A. I'm just looking at this a little bit more carefully. So this is -- this is a different patent. This is the '845 patent, not the '775 patent, correct?

Q. It's part of the '777 (sic) file history. Let me ask you --

A. I'm sorry. Patent No. 7. I'm sorry. I was looking at the wrong number there. It was the application number.

So it is part of the '775, that's correct.

Q. Dr. Adams, we'll have to try not to talk over each other, or the reporter is going to kill us both, okay?

A. Okay.

Q. So --

A. I'd rather that that doesn't happen.

Q. -- if you let -- if you let me finish --

THE COURT: And then if she gets upset, you know, then I really get red in the face, and that's not good.

Q. (By Mr. Lee) So you're going to have --

A. Let's avoid that.

Q. Let me finish, and I promise you that I'll let you finish, okay?

THE COURT: Y'all are doing a good job of trying --

MR. LEE: All right.

THE COURT: -- so that's why I'm not getting involved.

So let's continue.

Q. (By Mr. Lee) Now, Dr. Adams, you understand what the file history is, do you not?

A. Yes, I do.

Q. You've reviewed the file history of the patent and patent applications leading to the '775 patent, have you not?

A. As you noted earlier, it's an extensive file history, so I went through things and tried to know where the changes were as best as I could.

Q. And the file history is the back and forth between the Patent Office, and in this case, Centocor, correct?

A. That is correct.

Q. All right. Now, at -- in DX777, I'm going to put on the screen a page, which in the bottom right-hand corner says 1339. It's an office action summary.

Now, you were here this morning when His Honor

described office actions, things the Patent Office did?

A. Hold on one second. I'm going to try to find that page.

Q. The bottom right-hand corner, you'll find the numbers that end 1339.

A. Yes. Thank you.

Q. Now, in this office action summary -- this is an office action by the Patent Office, correct?

A. Give me a moment, please.

That is correct.

Q. And if you go down to the line that's numbered 6, you will see that what the Patent Office has said is all the claims listed there are rejected.

Do you see that?

A. That is correct.

Q. Now, Centocor responded to that rejection, did it not?

A. That is my understanding. That is typical. It's what my laboratory -- what de do with the patents that my laboratory is filing as well.

Q. Okay. When you get a rejection, you respond and you try to change -- amend your claims so that you can satisfy the Patent Office, correct?

A. You try to be responsive to the Examiner, yes, that is --

Q. All right.
A. That's your task.
Q. So let's look at what Centocor did.
MR. LEE: Can I have first Page 1339 -- oh, I'm sorry. 1369.
Q. (By Mr. Lee) Do you have that in front of you?
A. I will in just a moment.
Now, once again, I glanced at these a long time ago, and so now I'm just doing my best to follow you.
Q. That's great.
A. Okay. Now that it is in front of me, yes.
Q. All right. You have it before you.
And this is an amendment that Centocor filed, correct?
A. Yes, that is correct.
Q. All right.
MR. LEE: Could we have Page --
Q. (By Mr. Lee) Get you to the right page.
MR. LEE: Could we have the page with the amended claims on it, please.
And could we blow up amended Claim 1.
A. Can you tell me which page? Oh, it's Page 12?
Q. (By Mr. Lee) Can you see it?
A. Okay. I see that, yes.

Q. So just so the jury understands, when -- and you know this from your experience -- when you have a claim and you're amending it, you cross out what you're eliminating, correct?

A. That is -- that is my understanding, yes.

Q. So here's what happened. Centocor had a claim pending that would have allowed infringement to be determined by competitive inhibition to either A2 or cA2, correct?

A. That would be the way I would read this.

Q. Right. But then in order to get the patent out of the Patent Office, they eliminated the reference to cA2, correct?

A. That is what it looks like.

Q. So the three sets of testing that you compared, which were Humira with cA2, is precisely the testing that Centocor told the Patent Office was no longer part of the claims, correct?

A. That is -- that is what it looks like.

Q. Right. And when you formed your opinion about competitive inhibition, did you consider the fact that Centocor had said, comparing cA2 to an isolated recombinant anti-TNF-alpha antibody is not what part of what we claim as our invention?

A. I'm sorry. Can you please repeat that?

Q. Sure. When you formed your opinion about infringement, did you consider that in order to get this patent, Centocor had said we're not going to include a claim that involves comparison of the competitive inhibition of a TNF-alpha antibody and cA2?

A. I don't believe that's something that I -- I cannot, to be honest to, remember whether I considered that, but I do not believe that I have.

Q. Would it be fair to say that you have made -- that the test you relied upon involving cA2 made precisely the comparison that Centocor said it would not make?

A. I don't know if it said it would not make. I'm not sure that that's what that language is. To be honest, I would not know if that's -- if that is what -- is the appropriate language here.

Q. Fair enough.

What we can agree is they eliminated any reference to cA2 in the claim, right?

A. I see that cA2 was crossed off as part of their response to the Examiner's -- the process of give and take with the Patent Examiner, correct.

Q. Now, let's go to the other tests, which were Ms. Tam's tests, correct?

And those tests did involve Humira and A2,

correct?

A. That is correct.

Q. And A2 is referred to specifically in the claims, correct?

A. That is correct.

Q. Now, the test was run by Ms. Tam, who has been a Centocor employee for a long period of time, correct?

A. Correct.

Q. There are independent labs that you have worked with before who could have run the test, correct?

A. That I've worked with or that I know of?

Q. That you know of. I'm sorry.

A. I know of independent labs that can run the test.

Q. And they could have run the test independently as an expert in the same way that you have given your opinions here, correct?

A. That is correct.

Q. Now, as you said, you reviewed the test for the first time about two years after they were done, correct?

A. And the first time they were done in 2006 or 2007? I don't recall.

Q. 2007.

A. So about a year -- just over a year after they

were done.

Q. Right. Now, Ms. Tam testified that her experiments involved showing that A2 affected the binding of Humira, correct?

A. She testified that they competed with each other for TNF-alpha.

Q. Well, one of them was labeled, correct?

A. That's correct.

Q. She labeled Humira, correct?

A. That is correct.

Q. And then she figured out, if she added increasing amounts of A2, what happened to Humira, correct?

A. She figured out how many of the Humira counts were read at the end of the experiment by the gamma counter, correct.

Q. She didn't label A2 and then put Humira in to see what happened if you ran the experiment in the reverse, correct?

A. That is correct. She did not do it that way.

Q. Now, the patent actually has a competitive binding test in it, doesn't it?

A. It -- I think I know where you're going. I'm not sure if it -- if -- it's not quite used in the way you're talking about it, but there is a competitive

binding test in it, that is correct.

Q. So -- and that test is shown at Figures 9A and 9B, correct?

A. That is correct.

MR. LEE: And let's bring up Figures 9A and 9B.

Q. (By Mr. Lee) Now, this is the patent itself, correct?

A. That is correct.

Q. This is the patent describing the concept of competitive inhibition, correct?

A. This is the patent that is showing the binding of, in this graph, A2 and chimeric A2, looking at them in terms of binding to TNF-alpha, that is correct.

Q. And the patent is trying to demonstrate that there is competitive inhibition between cA2 and A2, correct?

A. My understanding is this figure is trying to demonstrate that chimeric A2 and A2 have identical -- or very, very much the same binding properties for TNF-alpha.

Q. Are these competitive binding tests or not?

A. They are competitive binding tests showing that the secondary antibody that's being used doesn't matter.

Q. Right. And when the -- when the submission was made to the Patent Office -- let's take it in part, so we're clear about it. Let's look at Figure 9A. Do you have that in front of you?

A. That's fine.

Q. In Figure 9A, they've labeled with this radioisotope A2 and then added increasing amounts of cA2.

A. No, that is not correct. They did not use radio labels in this assay at all.

Q. Oh, let's do it then -- let's be precise. A2 was labeled, correct?

A. No. A2 was not labeled.

Q. So --

A. A2 was not modified.

Q. -- is it your testimony that there was no label at all on A2?

A. It is my testimony that neither of these antibodies in these assays were labeled. I've studied this in detail.

Q. Okay.

A. And, in fact, what they did -- and as I said, they were using this assay to demonstrate the -- that the secondary antibodies that were being used to detect A2 and chimeric A2 were working equivalent, because A2

is a mouse antibody, and chimeric A2 is a chimeric antibody.

Q. Let's just look at what the curve says. So let's put up 9A and 9B side by side.

In 9A, the axis at the bottom --

MR. LEE: May I approach the screen, Your Honor?

THE COURT: Certainly.

Q. (By Mr. Lee) In 9A, the axis at the bottom is chimeric A2, correct?

A. Correct. That means that they were increasing amounts of --

Q. Dr. Adams --

A. I'm sorry.

Q. -- does it say chimeric A2?

A. It does say chimeric A2, yes.

Q. And then at the top, it talks about what's being added, and it's A2, correct?

A. So --

Q. Is that right?

A. That is a fixed amount of A2 being added and increasing amounts of chimeric A2 being added as you go to the right across the bottom of the curve. I just want to be clear on what we're talking about here.

Q. Right. And then we get to 9B, and it's run in

the reverse. You have A2 on the bottom axis, correct?

A. Increasing concentrations of A2 being added, that is correct.

Q. And a fixed ailment of cA2, correct?

A. That is correct.

Q. So when the inventors wanted to describe to the Patent Office what it was doing -- what they were doing, they ran the tests in both directions, correct?

A. So when I spoke with Dr. Ghrayeb about this earlier today --

Q. Dr. Adams, my question is, when the inventors applied to the Patent Office and wanted to tell them what they did, what they gave the Patent Office was two sets of tests, one running it in one direction, and the other running it in the other --

A. Well, when they --

Q. -- is that correct?

A. -- when they wanted to show that there was no difference in the secondary antibody, that is precisely what they did, yes.

Q. All right. Now, you're also familiar with an article by Dr. Moller, correct?

A. That is correct.

MR. LEE: Could I have DX112, which is in evidence, Your Honor?

Q. (By Mr. Lee) And it's at Tab 2.
A. Tab 2? Thank you.
Q. And I'm going to ask you about that competitive test that Dr. Moller did.
You're familiar with DX112?
A. Yes, I have read this article.
Q. Right. And DX112 is an article that concerns what happens in murine anti-TNF-alpha antibodies, correct?
A. That is correct.
Q. It's an article by Achim Moller, correct?
A. Yes.
Q. It was published in 1990, correct?
A. Correct.
Q. Dr. Moller is a scientist who works for Abbott, correct?
A. That is what I heard.
Q. And the article back in 1990 referred to two different antibodies, one called mAB 195 and one called mAB 114 --
A. Correct.
Q. -- right?
And the article describes competitive inhibition testing or how one would influence the other, correct?

A. Those are two different things, but that is correct.

Q. All right. Now, let me bring up DX112 at Page 843.

A. Oh, I'm sorry. The Abbott number 843.

Q. Yes. I'm sorry.

You see there are some figures?

A. Yes, I do.

Q. Now, the conclusion that Dr. Moller reaches in 1990 about these tests involving an anti-TNF-alpha antibody is, mAB 114 has an influence on mAB 195 binding site but not vice versa.

A. But that's not a conclusion. That's in the results section.

Q. Is that what it says?

A. In the result section, not his conclusion.

Q. Okay. So the result that's reported is that mAB 114 has an influence on mAB 195 binding site but not vice versa, correct?

A. And then he concludes that there is no competition.

Q. Well, actually, let's see how one of ordinary skill -- how one would read this.

You testified that you have relied upon Dr. Tam's testing, correct?

A. I relied upon Dr. Tam's testing, that is correct.

Q. Right. And did you know that Dr. Tam concluded that these charts and this data demonstrate that the two antibodies compete in one direction but not the other?

A. Dr. Tam was shown the figure without given time to read the article, and then based on that, in a two-minute span or something like that during her deposition, under those limited conditions, which she then corrected later on in the deposition, said that it seems like it concludes, yes.

Q. Right. So when Dr. Tam, who had run competitive inhibition testing, was shown Dr. Moller's article, she looked at the article at the deposition -- correct?

A. She looked at the figure at the deposition. She did not have time to read the article.

Q. And she testified under oath that what was shown was competitive inhibition in one direction but not the other, correct?

A. That in that brief review, that would be the way she would conclude.

Q. Right. Now, if you had run the test in both directions, how much additional time would it have

taken?

A. Are you talking about Moller?

Q. No. I'm sorry. Let's go to Dr. Tam's test, which you agree with me were only run in one direction, correct?

A. That is correct.

Q. How much time would it have taken to run the test in the other direction?

A. A few more days.

Q. Right. How much would it have cost to run the test in the other direction?

A. That would be minuscule.

Q. Right. Now, if you had run it in the other direction, you then would have known whether there was a difference in the testing if you went in direction A from the testing if you went in direction B, correct?

A. That could have given you that result, yes.

Q. Right. If you had done the testing that the patent describes, going in both directions, you would have had that information, correct?

A. I disagree that the patent describes that, sir.

Q. But in any event, if you had done the testing both directions, you could tell us whether there was competitive inhibition in both directions, correct?

A. Yes, that is correct.

Q. All right. But you can't tell us that today, can you, sir?

A. In a one-word answer, no.

Q. Right. Thank you.

MR. LEE: Nothing further, Your Honor.

THE COURT: Redirect?

MS. MULLIN: A few questions, Your Honor.

REDIRECT EXAMINATION

BY MS. MULLIN:

Q. Dr. Adams, I think Mr. Lee asked you a few questions about whether you had ever done any experiments with the particular -- with TNF in particular. I forget -- I'm sorry. I forget the precise questions.

In terms of competition assays, do you have to develop a different assay for each different antigen or for each different antibody and each different time that you're testing?

A. Not typically. There's a few very, very strange targets, which are very large, heavily glycosylated molecules, such as mucins, where this may become a factor but not with molecules like this, no. There's very standard testing that's done.

Q. Prior to the time that you were asked to

consider information in this litigation, have you had any experience with interpreting data in competition assays?

A. Yes. I've been interpreting this data since 1985.

Q. And did you consider the protocol that Ms. Tam used before you relied on her data?

A. Of course.

Q. And did you consider the quality of her data before you relied on it?

A. Of course.

Q. And was there anything in there that suggested to you that there was anything unreliable about the data that was generated by Ms. Tam or the protocol or procedure that she used for her tests?

A. No. In fact, it was all very clear. The protocol was clearly laid out. The data was clear. It came from the instrument that read it, so there was no manipulation of the data. The calculations were there. It was beautiful. I wish my lab worked that way.

Q. As part of your job, do you have any experience -- or as part of any of the work you do, not even necessarily directly for Fox Chase Cancer Center, do you have any experience reviewing other people's work?

A. Yes, extensive experience. I'm a sitting member of the National Institute of Health study section that reviews grant applications from scientists from universities and cancer centers around the country. I review those grants. I decide -- help decide the National Institute of Health decide whether or not to fund the research.

Before that, I was a sitting member of the American Cancer Society's clinical cancer and immunopathology study section. I did the same thing there.

I've reviewed for the California Breast Cancer Program. I review articles that scientists submit to journals. My -- if you look in my CV, I've reviewed for probably 25 different journals over the years.

And I'm also on the editorial board of a couple of journals as well, where I'm involved in that process as well.

Q. And generally, do scientists -- are they in a position to rely on data that's generated by other people, even if they didn't do the tests themselves?

A. When you -- when you critically review it, yes, you have to look at it. If there's a problem with the data, we send it back. We reject the article or we don't fund the grant.

And so I'm very used to looking at this sort of stuff.

Q. Okay. I'd like then -- Mr. Lee asked you some questions about what's been marked as Defendant's Exhibit 777.

MS. MULLIN: Mr. Ficocello, can you bring up Defendant's Exhibit 777?

Q. (By Ms. Mullin) I'm going to point you to some specific pages, because this is the prosecution history, and there's a -- it's a big chunk of documents, Dr. Adams, okay?

A. Thank you.

Q. Mr. Lee asked you some questions about some changes that were made to the specification concerning testing with A2 or cA2?

A. That is correct.

Q. To the best of your recollection, was there ever any suggestion by the Examiner or by someone at Centocor that that change was being made because the testing for competition made a difference, whether you used A2 or cA2?

A. No, not at all.

Q. Okay. If I can refer you then to what has been marked as Page ABT01371343.

A. Okay.

MS. MULLIN: I don't think we have the right exhibit.

A. I do.

Q. (By Ms. Mullin) Okay. I'm not sure that he'll be able to bring it up on the screen, so maybe I can --

MS. MULLIN: Oh, he did. One, two, three -- fourth paragraph down, can you enlarge that for us on that page?

Q. (By Ms. Mullin) Now, this is part of what the Examiner was talking about in terms of the claims that -- and issues that had come up with respect to A2 and cA2.

And do you understand what this is referring to here?

A. Yes, I do. This is part of what I was asked to consider.

So what this means is that -- and if I'm misinterpreting it, it's just possible that I don't see.

Q. Well, at the very least, just to start with, just read, what did the Examiner say here?

A. So what the Examiner said is, Amendment of the specification to recite the date of deposit and the complete name and address of the depositor is required. "As an additional means for completing the record, applicant may submit a copy of the contract with the

depository for deposit and maintenance of each deposit.

And what this means is that, once again -- remember, I mentioned the ATCC, the American Type Culture Collection, which is that library that scientists put cell lines into that other cells -- other scientists can then request the cell lines.

So it's my understanding that Centocor deposited the cell line that makes A2 into this library so other scientists could get it back for testing. It is my belief, if I'm recalling correctly, that the cell line for chimeric A2 was not deposited in that repository.

So, therefore, it would not be easy for somebody else in the field to get chimeric A2, as easy as for it to get A2 to test the antibodies.

So the Examiner, in my opinion was saying, look, you only deposited A2 in the ATCC. That should be your test for the purpose of the words in the patent.

Q. So if you could turn then to what's been marked as ABT01371371.

A. Okay.

Q. The paragraph that starts with as examples of antibody. This is part of the response that Centocor gave to the Examiner, and this is part of the explanation for why the reference to cA2 was changed in

the claim language during -- in this application, right?

A. That is correct.

Q. And I think this is what you were just talking about, right?

A. That is exactly what I was just talking about.

Q. So in your review and in your opinion, was there any substantive decision about whether or not A2 and cA2 was interchangeable in assays, or is this a paperwork kind of issue with respect to a depository?

A. So in my opinion, the Examiner was not stating that cA2 is not appropriate. He was just talking about whether it had been deposited.

Q. Okay. Now, I'd also like to pull up -- I believe Mr. Lee pointed you to a specific part of Defendant's Exhibit 112, which is the Moller reference. And if you could look --

MS. MULLIN: Mr. Ficocello, a page that ends in 843, just the next page.

And if you can just keep going a little bit more down.

Okay. Stop, okay? Actually, if you can go a little bit more down, that would be great.

Stop.

May I walk over here -- more than arm's length, Your Honor?

THE COURT: Yes.

MS. MULLIN: Okay. Thank you.

THE COURT: It's not quite that strict.

MS. MULLIN: Okay.

THE COURT: I haven't shot anybody yet for moving to the screen. But Mr. Beck hasn't got up yet, so...

MS. MULLIN: Okay.

Q. (By Ms. Mullin) Now, in his questions to you, Mr. Lee pointed to something over here that says mAB 114 has an influence on the mAB 195 binding sites but not vice versa, right?

A. That is correct.

Q. That doesn't say competition, does it?

A. No. In fact, when I was reading -- oh, okay. Go ahead.

Q. Well, let's look over here and see what was actually said by the authors about competition.

MS. MULLIN: Mr. Ficocello, if you could highlight those two sentences in this paragraph, please, starting there.

A. I suggest that the epitopes are not in close proximity, and mAB 195 could not compete with the other mABs tested suggesting -- is that what you mean?

Q. (By Ms. Mullin) Right. So let me just stop.

There's a difference here between talking about whether or not there's an influence in an assay done one way but not the other way and whether there's competition, right?

A. That's what I told Mr. Lee. The authors did not conclude that those were the same things. They were using those words to mean very different things.

Q. Okay. And then you were talking about the '775 patent, Plaintiff's Exhibit 1, and specifically about Figures 9A and 9B.

A. That is correct.

Q. And I think there was a suggestion that there was a reason that in the patent, the assay was done -- I think Mr. Lee was trying to suggest in both directions, right?

A. That is correct.

Q. But you mentioned something about secondary antibodies, and can you just explain, were these assays done both ways because it was necessary to show competition or for some other reason?

A. So I read this in detail.

I also spoke with the inventor about this to ask precisely why it was done this way, and what he said was, once again, as I pointed out to Mr. Lee, these antibodies were not tagged. They were not labeled with

radioisotopes or any other tag. So they had to use a different antibody to detect them, to detect them on the plate.

And the way scientists do that is they take -- they use what we call a secondary antibody, often made in a goat. It's a polyclonal antibody, which means that it binds to many spots. And the quality can differ from a goat anti-mouse polyclonal antibody to a goat anti-human polyclonal antibody.

So the authors of the patent felt it was necessary to show that the detection done with the goat anti-mouse polyclonal antibody gave a reliable result, but they also felt that they needed to show that the detection done with the goat anti-human polyclonal antibody also gave a reliable result, because they had not directly labeled the antibodies used.

Q. And finally, I think Mr. Lee tried to suggest that Ms. Tam drew some kind of conclusions based on the Moller reference that are not consistent with what you just said.

And since you referred to her deposition, I think a copy's been provided to you.

A. Yes, I have a copy here.

Q. Okay. And if you can look at Ms. Tam's deposition at Page 209.

A. Okay.

Q. About Line 7, and it continues on to Page 210 to Line 5.

Now, she was asked a series of questions about the Moller reference, Figure 1, in particular, right?

A. That is correct.

Q. And what were the circumstances under which she was asked to draw conclusions?

A. So as part of doing -- preparing for this, I've lived through two depositions myself. And I can tell you that it's not unusual to be shown a document you've never seen before, and then you say, I've never seen it before, and the attorney says, well, take a quick look and make a conclusion, and you say, well, I'm doing my best.

So what -- she was asked: Have you ever seen this paper before?

And she said: I have not.

Have you had a chance to consider all the data that's presented in this paper?

No. This is -- no. I just barely got through Figure 1.

So I mean, I'm not sure how somebody can conclude that she's properly reviewed a paper -- as a scientist, you don't make a conclusion based upon one

picture.

You read how it was done; you weigh the methods that were used; you look at the results; and then you look at the conclusion that the scientist who wrote the paper did.

And we haven't even gone to the conclusions of the paper in all these discussions. That's not the proper way to treat a scientific paper.

Q. So after the questions that you were asked by Mr. Lee, Dr. Adams, has your opinion changed at all --

A. No.

Q. -- about whether or not the Humira antibody competes with A2 for binding to human TNF-alpha?

A. To me, it's obvious that they compete. It's not even clear; it's obvious. They compete.

MS. MULLIN: Thank you, Your Honor. Pass the witness.

THE COURT: Mr. Lee?

MR. LEE: Just a few questions, Your Honor.

Could I have the '775 patent up?

I'm sorry. We have to switch, Your Honor.

THE COURT: Certainly.

MR. LEE: Could we bring up the '775

patent at Column 48, Line 58, at the bottom?

RECROSS-EXAMINATION

BY MR. LEE:

Q. Now, you've just described to us what the inventors told you or what Mr. Ghrayeb told you about Figures 9A and 9B. Let's see what the patent says and what Centocor told the public about Figures 9A and 9B. So you'll see at the bottom of Column 48 something called Example 10, correct?

A. That is correct.

Q. And if you turn to the top of Column 49, there's a specific reference in the first four lines to Figures 9A and 9B.

Cross competition for TNF antigen was observed in this solid-phase ELISA format, Figures 9A and 9B, correct?

A. That is correct.

Q. This finding is consistent with the expected identical epitope specificity of cA2 and murine A2, correct?

A. That's right. That's exactly what I was saying, yes.

Q. Right. That's what the patent says, correct?

A. Yes. That's very clear.

Q. Right. And when you told us what Dr. Moller

concluded, the one thing we can agree is this: He conducted the test in both directions, correct?

A. He did conduct them in both directions, yes, that is correct.

Q. And you did not, correct?

A. I did not conduct any tests.

Q. Okay.

A. I already told you that.

MR. LEE: Nothing further, Your Honor.

THE COURT: Anything further?

MS. MULLIN: No, Your Honor. Thank you.

THE COURT: Okay. All right. You may step down.

THE WITNESS: Thank you, Your Honor. Should I give these to somebody?

THE COURT: Just leave everything right there, Doctor. You're fine.

All right, Ladies and Gentlemen. We're going to -- I know that you want to hear another witness and go to 5:30, but I'm not going to let you do that. I'm going to release you until in the morning.

Now, this is the first day of trial, and I know that you've heard some technical things and -- but what you don't want to do tonight when you go home and you talk to some friend or your spouse or someone

that you're talking to, and they say what are you doing, and well, of course, your spouse knows you're down here and down on a jury in the federal court in Marshall. The most likely question that follows from the person you're talking to is, what kind of case is it? Don't answer -- don't ever answer that question. You're instructed not to discuss the case. Because after some 43 years of doing this -- it's not quite as many as Mr. Beck, but --

MR. BECK: Thank you, Your Honor.

THE COURT: Got to pick on somebody here who knows it's all in good fun.

They're going to say, you know, I read something about antibodies, or I know something about that, or I talked to somebody, and you're beginning to hear something you don't need to hear.

And we got to decide this case solely upon the witness testimony and the exhibits and the admissions and stipulations that you have had read to you. So please don't do that.

And again, I caution you about making any type of internet search, looking at dictionaries. Don't do that. And have a nice evening, and I'll see you in the morning. Drive safely. 8:30.

COURT SECURITY OFFICER: All rise.

(Jury out.)

THE COURT: All right. Please be seated.

Anything we need to take up from the Plaintiff at this time?

MR. SAYLES: Your Honor, I don't know of anything we need to take up.

THE COURT: Okay. Anything over here?

MR. BECK: No, Your Honor.

THE COURT: All right. Mr. Sayles, tomorrow will be your day to be picked on. I mean, I can remember when you had dark hair, but you were actually younger than either one of us. It's just the work's been harder on you.

MR. SAYLES: Well, you said he's been around a lot longer than you have. I've been around a whole lot less.

THE COURT: I know. I know. But I just thought I'd just forewarn you.

Mr. Beck knew I was going to pick on him today, so I'll just forewarn you, tomorrow is your day in the box.

MR. SAYLES: Yes, sir.

THE COURT: Let's see. I don't think I have anything for you either.

So as you know, if something comes up in

your exchange of whatever you're going to do tomorrow on the witnesses, I try to be in chambers by 8:00 o'clock every morning. So if you need to see me, let's try to make sure we raise any matters, you know, then rather than slow down our progress.

And in case you're interested, the Plaintiff has used 3 hours and 29 minutes, and the Defendant has used an hour and 27 minutes.

COURT SECURITY OFFICER: All rise.

(Court adjourned.)

* * * * * *

CERTIFICATION

I HEREBY CERTIFY that the foregoing is a true and correct transcript from the stenographic notes of the proceedings in the above-entitled matter to the best of my ability.

/s/_____ _____
SUSAN SIMMONS, CSR Date
Official Court Reporter
State of Texas No.: 267
Expiration Date: 12/31/10

/s/_____ _____
JUDITH WERLINGER, CSR Date
Deputy Official Court Reporter
State of Texas No.: 731
Expiration Date 12/31/10